COMPETITION BETWEEN ORIGINATORS AND GENERICS: PUBLIC REGULATION AND INCENTIVES TO INNOVATE

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KEY WORDS

Competition, generics, innovation, originators, pharmaceutical markets, pricing, reference pricing, relevant market, risk-sharing schemes

MOTS-CLES

Accords de partage de risques, concurrence, génériques, innovation, fixation des prix, marchés pharmaceutiques, princeps, système de prix de référence

KEYWÖRTER

Generika, Innovation, Festbetrag, Originalpräparate, pharmazeutische Märkte, Preisfestsetzung, Vereinbarungen zur Risikoteilung, Wettbewerb,

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ABPI: Association of the British Pharmaceutical Industry

ACE: Angiotensin Converting Enzym

ACS: Acute Coronary Syndrome

ADC: Autorité De la Concurrence

AFSSAPS: Agence Française de Sécurité Sanitaire des Produits de Sante

AIFA: Agenzia Italiana del Farmaco

AME: Average Marginal Effect

AMG: Arzneimittelgesetz

AMNOG: Arzneimittelmarktneuordnungsgesetz

ANSM: Agence Nationale de Sécurité du Médicament et des Produits de Santé

API: Active Pharmaceutical Ingredient

ARS: Agence Régionale de Santé

ASMR: Amélioration du Service Médical Rendu

ATC: Anatomical Therapeutical Chemical

ATU: Autorisation Temporaire d'Utilisation

CAPI: Contrat d'Amélioration des Pratiques Individuelles

CCB: Calcium Channel Blockers

CED: Coverage with Evidence Development

CEPS: Comite Economique des Produits de Sante

CJEU: Court of Justice of the European Union

CPR: Comitato Prezzi e Rimborso

CTS: Commissione Technico Scientifica

DoH: Department of Health

EC: European Commission

ECJ: European Court of Justice

ECMR: European Community Merger Regulation

EDMA: European Diagnostics Manufacturers Association

EEA: European Economic Area

EFPIA : European Federation of Pharmaceutical Industries and Associations

EMA: European Medicines Agency

EphMRA: European Pharmaceutical Marketing Research Association

EUnetHTA: European Union Network of Health Technology Assessment

FTC: Federal Trade Commission

G-BA: Gemeinsaner Bundesausschuss

GDP: Growth Domestic Product

GHS: Groupes Homogènes de Séjour

GKV: Gesetzliche Krankenversicherung

GKV-WSG: GKV-Wettbewerbsstärkungsgesetz

GKV-GMG: GKV- Modernisierungsgesetz

GSK: GlaxoSmithKline

HAS: Haute Autorité de Santé

HTA: Health Technology Assessment

H2RA: H2 Receptor Antagonist

INN: International Non Proprietary Name

IQWiG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IVD: In-Vitro Diagnostic

LEEM: Les Entreprises du Médicament

LFSS: Loi de Financement de la Sécurité Sociale

LMWH: Low Molecular Weight Heparin

ME: Marginal Effect

MEM: Marginal Effect at Mean

MER: Marginal Effect at Representative Value

ML: Maximum Likelihood

MLE: Maximum Likelihood Estimator

NACE: Statistical Classification of Economic Activities in the European Community

NCE: New Chemical Entities

NHS: National Health Service

NICE: National Institute for Health and Clinical Excellence

NME: New Molecular Entities

NRT: Nicotine Replacement Therapies

OECD: Organisation for Economic Co-operation and Development

OFT: Office of Fair Trading

ONDAM: Objectifs Nationaux des Dépenses d'Assurance Maladie

OTC: Over-The-Counter

PAS: Patient Access Schemes

PPI: Proton Pump Inhibitor

PPRS: Pharmaceutical Price Regulation Scheme

PVA: Price Volume Agreement

QALY: Quality-Adjusted Life Year

RTU: Recommandation Temporaire d'Utilisation

Rx medicinal product: Medicinal product subject to medical prescription

SGBV: Sozial Gesetzbuch V

SMR: Service Médical Rendu

SSN: Servizio Sanitarto Nazionale

SSNIP: Small but Significant and Non-transitory Increase in Price

SSRI: Selective Serotonin Reuptake Inhibitor

T2A: Tarification A l'Activité

TFEU: Treaty on the Functioning of the European Union

TFR: Tarif Forfaitaire de Responsabilité

UFH: Unfractioned Heparin

VBP: Value-Based Pricing

VRS: Velcade Response System

WHO: World Health Organisation

SUMMARY

The aim of this thesis is to examine the competition patterns that exist between originators and generics by focusing on the articulations between regulation and incentives to innovate. Once the characteristics of regulation in pharmaceutical markets is reviewed in the first chapter and an analysis of some current challenges related to cost-containment measures and innovation issues is performed, then in the second chapter, an empirical study is performed to investigate substitution patterns. Based on the EC´s merger decisions in the pharmaceutical sector from 1989 to 2011, this study stresses the key criteria to define the scope of the relevant product market based on substitution patterns and shows the trend towards a narrower market in time. Chapters three and four aim to analyse in depth two widespread measures, the internal reference pricing system in off-patent markets, and risk-sharing schemes in patent-protected markets. By taking into account informational advantages of originators over generics, the third chapter shows the extent to which the implementation of a reference price for off-patent markets can contribute in promoting innovation. Finally, in the fourth chapter, the modeling of risk-sharing schemes explains how such schemes can help in solving moral hazard and adverse selection issues by continuously giving pharmaceutical companies incentives to innovate and supplying medicinal products of a higher quality.

RESUME COURT

Dans une économie mondialisée sur un secteur très concurrentiel, ce travail de recherche articulé en cinq parties propose d'étudier de nouveaux schémas de concurrence entre médicaments princeps et génériques au sein de l'Union Européenne, en intégrant les articulations entre régulation publique et incitations à innover. Dans une première partie introductive, les spécificités règlementaires très évolutives des marchés pharmaceutiques sont présentées ainsi que leurs conséquences induites sur les systèmes de prix et l'innovation.

La deuxième partie, vise à analyser dans un premier temps l'approche adoptée par la Commission Européenne et les autorités de concurrence des divers Etats membres quant à la définition du marché pertinent de produits sur ces marchés. Plus particulièrement, dans un second temps, une étude empirique des schémas de substitution existants est développée à partir des décisions prises par la Commission Européenne de 1989 à 2011 en matière de fusions dans le secteur concerné. Cet examen des différents critères retenus pour définir la taille du marché pertinent souligne la tendance lourde à définir des marchés pertinents de produits toujours plus étroits, atteignant même le niveau moléculaire.

Dans la troisième partie, l'analyse du système de prix de référence mis en place dans de nombreux Etats membres sur ces marchés concurrentiels, montre, en prenant en compte les avantages informatifs des princeps, dans quelle mesure la mise en place d'un tel système, peut favoriser l'innovation.

Sous la quatrième partie, la modélisation de l'impact des nouveaux modèles d'accords de partage de risques se propose d'étudier comment de tels accords peuvent résoudre les problématiques d'aléa moral et de sélection adverse sur ces marchés, en incitant les entreprises à investir dans leur produit et à renforcer la qualité des biens fournis.

Enfin, la partie cinq conclut le travail en mettant en perspective les résultats obtenus et en analysant les conséquences sous-jacentes pour les politiques publiques.

RESUME LONG

CONCURRENCE ENTRE MEDICAMENTS PRINCEPS ET GENERIQUES: REGULATION PUBLIQUE ET INCITATIONS A INNOVER

1. Introduction aux marchés pharmaceutiques

Sous cette première partie, les différentes caractéristiques de la régulation des marchés pharmaceutiques, puis l'articulation entre régulation et incitation à innover sont exposées afin de pouvoir dégager les trois grandes thématiques, qui font l'objet de ce travail.

Dans une première section, les spécificités de la demande du marché sont décrites au travers de la théorie de l'agence. Ainsi, les conséquences de la limitation de l'accès liée à la prescription médicale et à la délivrance des médicaments en pharmacie, et les effets de hasard moral induits par les systèmes de sécurité sociale sont examinés de manière détaillée. En effet, les caractéristiques particulières des marchés pharmaceutiques s'expliquent par l´éclatement de la demande, entre le médecin qui prescrit, le pharmacien qui délivre, le ou les organismes assureurs qui remboursent et en dernier lieu, le patient qui «consomme» le médicament.

Concernant la régulation des prix, le marché pharmaceutique se différencie des autres marchés par ses spécificités de systèmes de prix et de remboursement qui dépendent des réglementations nationales, des différents régimes d'assurance maladie, d'un système européen de protection par les brevets, sans omettre une législation de sécurité sanitaire qui intègre la dimension de protection industrielle. Ces régulations propres entraînent la formation de deux marchés ayant des schémas de concurrence différents. Alors qu´une concurrence au niveau thérapeutique se renouvelle sans cesse pour les médicaments sous brevet, l´arrivée de versions génériques entraîne une concurrence par les prix, qui est également promue par un ensemble de mesures visant à limiter la croissance des dépenses de santé.

Sous une deuxième section, l'articulation entre régulation publique et incitations à innover rencontrées sur les marchés pharmaceutiques est étudiée. Sur le marché hors brevet, des barrières à l'entrée des génériques existent en raison de l´avantage des médicaments princeps en termes d'information et d'utilisation du produit par le médecin et le patient. Celles-ci sont renforcées par les stratégies des industriels qui lancent leurs propres génériques à côté des princeps. Sur le marché des médicaments sous-brevet, des méthodes d´évaluation pharmaco-économiques, utilisées de manière croissante par les organismes nationaux (ou locaux) responsables de la fixation des prix et du remboursement créent une barrière supplémentaire d´accès au marché.

La dernière section pose trois grandes questions concernant le fonctionnement économique des marchés pharmaceutiques, articulées entre réglementation publique et incitations à innover, questions auxquelles il est proposé de répondre au cours de ce travail.

1. Comment définir les schémas de substitution entre les médicaments?

Cette interrogation constitue de manière indirecte la base des liens entre régulation et incitations à innover. En effet, les différentes mesures prises visant à contenir la croissance des dépenses ont pour objectif de favoriser un usage rationnel des biens de santé, notamment par l´usage de génériques sur les marchés hors brevets, ou bien en restreignant le remboursement des médicaments innovants sous brevet aux alternatives thérapeutiques dont le ratio coût-efficacité est le meilleur. Toutes ces mesures impliquent que les produits concernés soient substituables entre eux. Toutefois, quels sont les critères de substituabilité appliqués et applicables?

La classification anatomique-thérapeutique-chimique (ATC) classe les produits selon leur indication (niveau 3), leur mécanisme d´action (niveau 4) et leur ingrédient actif (niveau 5). L´analyse du marché pertinent de produits qui est réalisée à l'occasion d'examen des fusions ou d'abus de position dominante utilise cette classification et renseigne ainsi sur les schémas de substitution au niveau de la demande et de l´offre de produits pharmaceutiques. A cet effet, la démarche de la Commission Européenne et de plusieurs autorités de concurrence nationales lors de fusions et d'abus de position dominante pour définir la notion de marché pertinent de produits est développée. Puis, une analyse économétrique des différentes décisions relatives à des fusions prises par la Commission Européenne depuis 1989, permet de déterminer les critères intervenant dans la définition de la taille de ce marché ainsi que son évolution.

2. Comment promouvoir la concurrence par les prix sur les marchés pharmaceutiques tout en donnant aux entreprises des incitations à innover?

Au sein de l'UE et des Etats membres, des éventails de mesures ont été pris afin de promouvoir l´usage des génériques et de favoriser la concurrence par les prix sur ce marché. Parmi celles-ci, figure le système du prix de référence qui fixe un prix maximum remboursable pour un groupe de produits pharmaceutiques considérés comme substituables et dont le brevet est échu, ou qui ne sont pas considérés comme innovants. Visant à augmenter l'élasticité de la demande au-delà de ce prix de référence, cette mesure promeut une concurrence par les prix sur les marchés pharmaceutiques, toutefois amoindrie par les avantages informationnels existants favorisant les princeps. Un tel mécanisme séparant médicaments innovants et ceux considérés comme non-innovants influe directement sur les marchés de produits sous-brevet. L'impact du système de prix de référence sur les incitations à innover, en prenant également en compte l'existence des avantages informationnels du princeps, est dans ce contexte, évalué.

3. Comment fournir aux patients un accès aux médicaments innovants tout en préservant l´équilibre des dépenses de santé?

Alors qu'une concurrence par les prix est encouragée sur les marchés dont le brevet est échu, celle sur les marchés de produits innovants repose sur la valeur thérapeutique des médicaments. Essentiellement, des évaluations pharmaco-économiques visent à déterminer la valeur ajoutée en terme médical. Toutefois, ces médicaments dont l´efficacité est souvent difficile à évaluer au regard de l'évolution rapide du marché et des incertitudes sur leur efficacité prouvée et sur la taille de la population-cible, sont coûteux pour les différents acteurs, en particulier, les organismes assureurs. L'examen des accords de partage de risques entre les organismes assureurs et les entreprises pharmaceutiques, permet de mesurer leur impact sur les problématiques d'aléa moral et de sélection adverse.

2. Analyse économique de la définition du marché de produits pertinents sur les marchés pharmaceutiques

Afin de répondre à la première question concernant les schémas de substitution, la première section traite de l'approche de la Commission Européenne et se propose d'identifier les différents participants sur le marché lors de fusions (règlement (CE) n° 134/2004) ou d'investigations en cas d'abus allégué de position dominante (article 102 du Traité FUE).

Après avoir expliqué la logique et les principes sous-jacents à la définition du marché pertinent de produits, les spécificités relevant des acteurs concernés et des caractéristiques institutionnelles sont analysées. Les trois principaux critères qui participent à la définition du marché pertinent choisi par la Commission Européenne sont également listés. Il s'agit, tout d'abord, de la distinction par le statut concurrentiel, c'est-à-dire, si les produits considérés sont protégés par un brevet ou ne le sont plus. En raison de leur bioéquivalence, les médicaments génériques sont ainsi considérés comme appartenant au même marché pertinent de produits que le princeps. Un deuxième critère concerne le critère de prescription, c'est-à-dire si les médicaments sont prescrits uniquement sur ordonnance ou peuvent être délivrés au patient sans ordonnance. Cette différence est importante car les médicaments vendus sans ordonnance ont souvent un dosage moins élevé que ceux vendus uniquement sur ordonnance. En effet, selon le dosage et la forme, les mêmes principes actifs peuvent relever de marchés pertinents différents. Enfin, le dernier critère de distinction concerne les spécificités du circuit de distribution, que ce soit à l'officine ou dans le cadre d'un séjour hospitalier. En effet, les mécanismes de fixation des prix et remboursement pour ces deux canaux de distribution diffèrent souvent.

La deuxième section, qui se base sur l'analyse effectuée dans la première section, porte exclusivement sur la réalisation d'une étude économétrique des décisions de la Commission Européenne relatives au périmètre des marchés pertinents du secteur pharmaceutique en analysant les décisions de fusion entre 1989 et 2011. Cette étude empirique, qui n'a encore jamais été pratiquée, étudie 217 marchés pertinents à l'aide d'un modèle utilisant la fonction « logit » et « ordered logit ». Elle permet d'étudier les critères sur lesquels la Commission Européenne se base pour définir le périmètre du marché pertinent de produits sur la base du système de classification ATC, et, pour un sous-échantillon 2004-2011, d´analyser les critères spécifiques qui expliquent le choix d'un périmètre toujours plus restreint, allant même jusqu'à considérer qu'un produit représente un marché pertinent à lui seul.

Dans un premier temps, concernant l'échantillon 1989-2011, en accord avec la Communication de la Commission sur la définition du marché en cause aux fins du droit communautaire de la concurrence (97/C 372/03), il ressort que la substituabilité au niveau de la demande est la base de la définition du marché pertinent en raison de son impact le plus immédiat sur la situation de concurrence. L'analyse montre que les critères conduisant à des pratiques de prescription particulières comme l'utilisation attendue du médicament, son mode de distribution, la présence de nouvelles molécules ou de produits vendus sans ordonnance contribuent déjà à s'écarter de l'analyse au niveau thérapeutique (ATC 3) et diminuer le périmètre du marché pertinent en prenant en compte le mécanisme d'action (ATC 4) ou l'ingrédient actif (ATC 5). Comme attendu, le rôle de la substitution au niveau de l'offre est moindre et celui de l'environnement politique inexistant.

Dans un second temps, le sous-échantillon 2004-2011 est analysé en détail. Les mêmes résultats concernant l'importance des schémas de substitution au niveau de la demande sont également visibles. De manière plus spécifique, l'utilisation du produit et les différences d'efficacité entre les produits sont les principaux critères pour limiter le périmètre du marché pertinent à l'échelon moléculaire (ATC 4). Toutefois, ce sont les critères relatifs à la substance active, au mode de distribution et à la forme galénique qui sont les critères principaux conduisant à définir un marché pertinent très étroit au niveau moléculaire (ATC 5). Il en va de même si le produit peut être délivré sans ordonnance en raison des particularités de la classification ATC. Une segmentation des marchés pharmaceutiques se dégage, d'une part entre les produits qui ne sont plus sous brevet dont les critères de substitution se situent au niveau thérapeutique (ATC 3) et d'autre part les produits innovants. Pour ces derniers, le marché pertinent est plus étroit et, selon le produit, il n'est pas rare qu´il se situe à l'échelon moléculaire, un produit constituant un marché à lui-même.

3. Prix interne de référence et ses impacts sur les incitations à innover

Après avoir procédé à la définition des différents niveaux de substitution, la troisième partie entend répondre au second questionnement sur les liens entre les mesures de limitation des dépenses de santé et les incitations à innover. Le système global de prix de référence, son mode de fonctionnement et ses effets sur l'innovation sont examinés en intégrant les distorsions en terme d´information qui favorisent les produits princeps afin de pouvoir dresser des hypothèses quant à la pertinence de la mise en place de telles mesures.

La première section se propose de définir le mécanisme du prix de référence interne en envisageant les diverses formes qu'il peut prendre dans les divers pays européens et en retenant en particulier les expériences allemande et française. Schématiquement, le système de prix de référence correspond à la fixation d'un prix maximum remboursé au patient, au-delà duquel ce dernier doit payer entièrement le reste à charge.

Dans une deuxième section, après l'analyse des principaux modèles théoriques (Zweifel and Crivelli, 1996; Merino-Castello, 2003; Brekke et al., 2007 and 2011; Bardey et al., 2011) et empiriques (Giuliani, 1998; Aronsson, 2001; Pavcnik, 2002, Grootendorst, 2002; Stargadt, 2010) dédiés au système des prix de référence dans la littérature économique, un modèle nouveau est proposé en intégrant l'avantage informatif des produits princeps. Par avantage informatif en faveur des produits princeps sont compris tous les avantages acquis par le produit princeps pendant la période d'exclusivité du médicament notamment la fidélité des médecins prescripteurs une fois le brevet échu ((Hurwitz and Case, 1988; Rizzo, 1999; Morton, 2000; Hellerstein, 1998; Cabrales, 2003; Königbauer, 2007). Il peut s'agir de l'effet de campagnes de publicité mais aussi de l'effet d'habitude de prescription d´un médecin. Cet avantage informatif en faveur des médicaments princeps, souligné dans de nombreuses études empiriques, est à l'origine d'une concurrence par les prix faussée entre médicaments génériques et produits princeps. Le modèle présenté montre comment l'introduction d'un système de prix de référence, en augmentant l'élasticité de la demande au-delà de ce prix de référence, permet de contrebalancer le biais créé par l'avantage informatif.

Alors que les modèles économiques théoriques existants se concentrent sur l'impact du prix de référence sur les prix et la santé des patients, dans la troisième section, en enrichissant le modèle précédent, une modélisation des interactions créées par la mise en place d'un prix de référence sur les incitations à innover a été envisagée. En se basant sur le modèle de Ganuza et al. (2007, 2009) et en intégrant au modèle précédent un terme prenant en compte l'innovation apportée au produit princeps, il est possible de montrer que l'impact du prix de référence sur le niveau d'innovation choisi par les entreprises dépend du niveau

d'investissement initial. Uniquement dans le cas précis où le niveau d'innovation choisi par les firmes est supérieur au niveau d'innovation social optimal, la mise en place d'un système de prix de référence est alors recommandée.

L'efficacité de cette mesure du prix de référence peut être renforcée par des politiques visant notamment à réduire l'hétérogénéité des médecins prescripteurs et à minimiser leur fidélité envers les médicaments princeps ainsi que l'impact de la publicité, agissant ainsi directement sur les politiques de santé. Après avoir observé comment le mécanisme du prix de référence était complémentaire des mesures prises sur le marché des médicaments encore sous-brevet, le modèle précédemment exposé est confronté à la réalité des mesures mises en place en Allemagne et en France. Il est possible d'en déduire que la mise en place du système de prix de référence, bien que différente dans les deux pays, s'est accompagnée de mesures similaires tendant à décroître la fidélité vis-à-vis des médicaments princeps et à réglementer leur publicité.

4. Analyse économique des accords de partage de risques sur les marchés pharmaceutiques

La quatrième partie se concentre sur l'accès au marché des produits innovants pour faire face aux besoins des patients. A cet effet, les accords de partage de risques sont analysés en mettant l'accent sur leur capacité à apporter une réponse aux problèmes d'aléa moral et de sélection adverse qui existent sur les marchés pharmaceutiques.

Une première section traite des différents types d'accord de partage de risques et la raison de leur existence. Suite à l'accroissement des exigences des autorités de santé pour une prise en charge par la collectivité, en particulier l'évaluation des technologies de santé qui amène à considérer l'ensemble des traitement alternatifs existants dans une optique d'optimisation budgétaire, l'accès au remboursement pour les médicaments innovants et coûteux est rendu plus difficile. Lors de ces évaluations des technologies de santé, le ratio coût-effectivité du médicament est calculé.

Toutefois, comme déjà défini lors du « High Level Pharmaceutical Forum » organisé par la Commission Européenne en 2005, l'effectivité d'un médicament fait référence à ses effets réels sur les patients traités alors que l'efficacité est basée sur les effets d'un médicament tels qu'évalués lors des essais cliniques sur des échantillons de patients définis selon des critères particuliers. L'effectivité d'un médicament peut ainsi différer de son efficacité et en règle générale est inférieure en raison des aléas du traitement réel. Ainsi, les organismes d'assurance et les entreprises pharmaceutiques peuvent s'engager dans des accords de partage de risques. Dans ces derniers, selon des modalités diverses, l'entreprise pharmaceutique garantit

l'effectivité du produit ou s'engage à ne fournir qu'un volume de produits prédéfini dans l'accord en contrepartie du remboursement de son produit. De tels accords permettent ainsi aux organismes assureurs de gérer l'incertitude autour d'un nouveau produit innovant tout en laissant la possibilité aux entreprises pharmaceutiques d'émettre un signal sur l'effectivité de leur produit. En prenant comme exemples les cas de l'Allemagne, de la France, de l'Italie et du Royaume-Uni, il s'avère que les modalités de mise en place des accords de partage de risques sont très variables selon les différents Etats membres. Après avoir décrit les grands principes de leur instauration, les accords de partage de risques sont analysés de manière théorique (Lilico, 2003; Zaric et al. 2003, 2009; Capri et al, 2011; Barros, 2011; Antonanzas et al. 2011) en prenant en compte les problématiques d'aléa moral et de sélection adverse présentes sur les marchés pharmaceutiques ce qui n'a pas encore été pratiqué ou réalisé.

Une deuxième section aborde l'impact des accords de partage de risques sur l'aléa moral. Ce dernier est présent du fait de la dissociation entre effectivité et efficacité. Etant donné la fixation des prix sur les marchés pharmaceutiques, une fois un médicament commercialisé, les entreprises ont moins d'incitation à investir pour innover sur ce produit. Pour étudier les cas où un accord de partage de risques est souhaitable à la fois pour l'organisme assureur et pour le bien-être des patients, un modèle avec une information distribuée symétriquement et asymétriquement est élaboré et les comparaisons effectuées selon, ou non, l'existence d'accord de partage de risques. Il ressort de ce modèle, qu'avec un mécanisme usuel de fixation des prix, l´organisme assureur ne peut octroyer aux entreprises d'incitations à innover. Un accord de partage de risques s'avère essentiel si l´organisme assureur souhaite promouvoir l´innovation. Toutefois, un tel accord n´est efficace que si l´entreprise pharmaceutique possède une information privée, c´est-à-dire si l´information est distribuée asymétriquement entre l´organisme assureur et l´entreprise pharmaceutique. Si la distribution est symétrique, ce qui revient à considérer que l´organisme assureur peut observer les efforts en termes de R&D effectués par l´entreprise pharmaceutique, un tel mécanisme de partage de risques est inutile.

Enfin, la troisième section étudie la sélection adverse qui, pour sa part, est présente en raison de l´incertitude de l´organisme assureur quant à l´effectivité d´un médicament en utilisation réelle. Une entreprise mettant sur le marché un médicament innovant est alors tentée de majorer l´effectivité de son médicament afin d´obtenir un prix plus intéressant. A l´aide d´un modèle de « signaling » qui laisse à l´entreprise le choix de proposer un accord de partage de risques à l'organisme assureur, il est possible de montrer, qu´en cas de distribution asymétrique de l'information entre l´organisme assureur et l´entreprise pharmaceutique et sous certaines conditions, un équilibre séparateur existe. De ce fait, uniquement une entreprise produisant un produit efficace proposera un tel accord alors qu´une entreprise proposant un produit moins efficace optera pour le mécanisme usuel de fixation des prix. Ainsi, le mécanisme de partage

de risques auxquels les Etats membres ont recours de manière croissante, en résolvant les problématiques liées à l'aléa moral et la sélection adverse, représente un moyen privilégié de donner aux patients un accès rapide aux médicaments innovants tout en préservant l´équilibre des dépenses de santé.

5. Conclusion: Quelles perspectives?

Ce travail reposant sur des analyses économétriques démontre la présence de deux marchés : marché de produits sous-brevet et de produits hors-brevet, ayant des schémas de concurrence et de régulation apparemment bien différenciés. L'analyse de deux mesures, le système du prix de référence et les accords de partage de risques, montre à quel point ces deux marchés sont interdépendants. Des politiques de régulation efficaces prenant en compte ces aspects gagnent à être développées, tant au niveau national qu'européen pour favoriser une meilleure harmonisation entre les systèmes de prix, une limitation de la croissance des dépenses, un meilleur accès aux soins pour tous les patients et encourager une Europe plus compétitive sur les marchés internationaux.

L'analyse effectuée a été menée sur les médicaments pharmaceutiques d'origine chimique. Etant donné le potentiel en termes médical et de croissance économique des médicaments biologiques, ainsi que leurs spécificités conduisant à des schémas de concurrence distincts des médicaments chimiques, ces derniers constituent un sujet de prédilection pour de futures recherches.

KURZFASSUNG

In dieser Arbeit werden erstmals die Merkmale der Regulierung auf Pharmamärkten beschrieben und die aktuellen Fragen bezüglich der verschiedenen Marktteilnehmer (Patienten, Ärzte, Krankenkassen) vorgestellt, die im Verlauf dieser Dissertation beantwortet werden: Was sind die Substitutionsmuster auf den Pharmamärkten? Wie kann Preiswettbewerb gefördert werden ohne die Innovationsanreize zu gefährden? Wie können Patienten mit innovativen Arzneimitteln versorgt werden ohne das Haushaltsbudget zu gefährden? Um die erste Frage zu beantworten wird in dem zweiten Teil dieser Dissertation die Definition der relevanten Marktabgrenzung auf Pharmamärkten untersucht. Hierbei wird die Praxis der Europäischen Kommission zur Marktabgrenzung im Bereich Fusionen durch eine ökonometrische Analyse untersucht, um die Substitutionskriterien ausführlich zu analysieren. Der dritte Teil dieser Arbeit untersucht die Funktion sowie die Auswirkungen eines internen Referenzpreissystems auf die Innovationsanreize von Pharmaunternehmen. Zu diesem Zweck werden zunächst die existierenden Verzerrungen im Wettbewerb zwischen Originalpräparaten und Generika betrachtet. Daraufhin sollen die Auswirkungen der Implementierung eines Referenzpreissystems erläutert werden. Die abschließenden Schlussfolgerungen unterstreichen die Relevanz eines solchen Systems, um Anreize für Innovationen zu setzen. Nach der Analyse des Referenzpreissystems für Produkte, die nicht mehr unter Patentschutz stehen, um den Preiswettbewerb zu stärken, bezieht sich der dritte und letzte Teil auf die Vereinbarungen zur Risikoteilung, die eine Alternative sind, um kosteneffiziente innovative Arzneimittel verfügbar zu machen. Zu diesem Zweck werden Vereinbarungen zur Risikoteilung theoretisch in Bezug auf Fragestellungen zu moralischem Risiko und adverser Selektion untersucht. Im weiteren Verlauf der Arbeit wird gezeigt, dass Vereinbarungen zur Risikoteilung wünschenswert sind, weil sie Firmen Anreize geben, im Laufe des Lebenszyklus eines Arzneimittels zu investieren. Dazu kann bewiesen werden, dass nur eine Firma mit einem effizienten Produkt eine Vereinbarung zur Risikoteilung anbieten würde.

Als Schlussbemerkungen werden weitere Forschungsaspekte, vor allem biologische Präparate, angesprochen.

AUSFÜHRLICHE KURZFASSUNG

WETTBEWERB ZWISCHEN ORIGINALPRÄPARATEN UND GENERIKA: ÖFFENTLICHE REGULIERUNG UND INNOVATIONSANREIZE

1. Einführung zur Regulierung auf Pharmamärkten

Der erste Teil dieser Dissertation, der als Einführungskapitel dient, beschreibt die Merkmale der Regulierung der Pharmamärkte und die aktuellen Fragestellungen bezüglich der verschiedenen Marktteilnehmer (Patiente, Ärzte, Krankenkassen).

Im ersten Abschnitt werden die Besonderheiten der betroffenen Akteure und der institutionellen Rahmenbedingungen analysiert. Auf der Nachfrageseite sind die Besonderheiten erstens mit Hilfe der Prinzipal-Agenten-Theorie zu verstehen. Eine Prinzipal-Agent-Beziehung zwischen dem Patienten und dem Arzt entsteht durch die zugangsbeschränkte Verordnung und Abgabe von Arzneimitteln. Zweitens spielt die Moral-Hazard-Problematik eine Rolle, da die Krankenkassen einen Teil der Gesundheitsausgaben übernehmen. Was die Angebotsseite betrifft, so unterscheidet sich der Pharmamarkt von den anderen Märkten durch sein einzigartiges Preis- und Erstattungssystem, das sowohl durch nationale Gesetzgebung, als auch durch die Rolle der Patente und der Gesundheitssicherungsregelung festgelegt wird. Diese Eigenschaften führen zur Entstehung von zwei Märkten mit verschiedenen Wettbewerbsmustern. Auf dem Markt für innovative patentgeschützte Produkte findet ein therapeutischer Wettbewerb statt. Der Markteintritt von Generika nach Patentablauf des Originalpräparats wirkt sich durch den Wettbewerb preissenkend aus. Dieser Preiswettbewerb wird ebenfalls mit den unterschiedlichen ergriffenen Kostendämpfungmaßnahmen gefördert.

Im zweiten Abschnitt werden die auf den Pharmamärkten auftretenden Probleme ausführlich beschrieben. Einserseits werden Zugangsbarrieren für Generika auf Märkten analysiert, auf denen die Patente abgelaufen sind. Diese Barrieren existieren aufgrund der Vorteile, die Originalpräparate gegenüber den Generika haben. Diese Vorteile sind vielfältig und stammen aus der Bekanntheit des Produktes bei den verschreibenden Ärzten durch Werbekampagnen oder durch die längere Erfahrung der Ärzte mit dem Produkt. Diese Zugangsbarrieren werden zusätzlich durch die Strategien der die Originalpräparate herstellenden Firmen verstärkt, die ihre eigenen Generika kurz vor dem Markteintritt der Generikafirmen einführen. Andererseits, in Bezug auf patentgeschützten Arzneimitteln, werden zunehmend gesundheitsökonomische

Analysen für innovative Produkte im Rahmen der nationalen Preis-und Erstattungsmechanismen durchgeführt. Solche Untersuchungen stellen zusätzliche Marktzugangsbarrieren für innovative Produkte dar.

Im dritten und letzten Abschnitt der Dissertation werden die folgenden drei Fragestellungen behandelt, die das wirtschafliche Tätigkeiten von Pharmamärkten betreffen und insbesondere sich auf die Schnittstelle von Regulierung und Innovationsanreizen beziehen.

1) Welche Substitutionsmuster charakterisieren die Pharmamärkte?

Diese Fragestellung bildet indirekt die Grundlage der Verknüpfungen zwischen Regulierung und Innovationsanreizen. Tatsächlich zielen die ergriffenen kostendämpfenden Maßnahmen darauf ab, den vernünftigen Gebrauch von Arzneimitteln zu fördern. Beispiele solcher Maßnahmen sind die Aufnahme von Generika auf patentabgelaufenen Märkten oder die Beschränkung der Zurückerstattung patentgeschützter Arzneimittel auf die therapeutische Alternative mit dem besten Kosten-Nutzen Verhältnis. All diese Maßnahmen gehen davon aus, dass die betroffenen Produkte substituierbar sind. Jedoch stellt sich die Frage, welche Substitutionskriterien anwendbar sind bzw. angewendet werden. Die Anatomisch-Therapeutisch-Chemische Klassifizierung (sogenannte ATC-Klassifizierung) ordnet die Arzneimittel gemäß ihrer Indikation (ATC-Niveau 3), ihres Wirkmechanismuses (ATC-Niveau 3) und ihres Wirkstoffes (ATC-Niveau 5) ein. Die Analyse des relevanten Produktmarktes, die im Rahmen einer Fusion (Verordnung (EG) Nr.134/2004) oder einer Untersuchung eines angeblichen Missbrauchs einer marktdominierenden Position durchgeführt wird, benutzt ebenfalls diese Klassifizierung und informiert dabei über die Nachfrage- und Angebotssubstitutionsmuster.

In dieser Hinsicht wird die Vorgehensweise der Europäischen Kommission in Sachen Marktabgrenzung untersucht und eine ökonometrische Analyse der Marktabgrenzungen aller EU-Fusionsfälle auf Pharmamärkten von 1989 bis 2011 durchgeführt. Ziel dieser Studie ist es, die Kriterien aufzulisten, die den Umfang des relevanten Marktes bestimmen und die Evolution dieses Umfangs in der Zeit zu erklären.

2) Wie kann Preiswettbewerb gefördert werden ohne Innovationsanreize zu gefährden?

Verschiedene Maßnahmen wurden in den Mitgliedstaaten ergriffen, um den Gebrauch von Generika voranzutreiben und damit den Preiswettbewerb zu fördern. Beispielsweise setzt das Referenzpreissystem (auch Festbetragssystem genannt) einen maximal zurückerstattbaren Betrag fest. Dies gilt für eine Gruppe von Arzneimitteln, die als substituierbar eingestuft werden und deren Patent abgelaufen ist oder die von den Gesundheitsbehörden als nicht innovativ bewertet wurden. Diese Maßnahme, die das Ziel verfolgt, die Nachsfrage elastizität jenseits des Referenzpreises zu erhöhen, fördert einen Preiswettbewerb, der durch die Informationsvorsprünge der Originalpräparate vermindert wird. Jedoch hat ein solcher Mechanismus, der innovative Arzneimittel von nicht-innovativen Arzneimitteln trennt und zu einem ver-

stärkten Preiswettbewerb führt, auch Auswirkungen auf die patentgeschützten Pharmamärkte. Bei der Berücksichtigung dieser Informationsvorsprünge ist das Ziel, die Wirkung dieses Mechanismuses auf Innovationsanreize zu untersuchen.

3) Wie können Patienten mit innovativen Arzneimitteln versorgt werden ohne das Budget zu gefährden?

Im Zuge der steigenden Kosten im Gesundheitswesen wurden in allen Mitgliedstaaten der Europäischen Union Maßnahmen ergriffen, die direkt oder indirekt Preise kontrollieren. Die in 2008 von der Europäischen Kommission durchgeführte Untersuchung des Arzneimittelsektors hat unter anderem auf die Notwendigkeit eines transparenteren Preis- und Erstattungssystems in Europa hingewiesen, das gleichzeitig Anreize zur Innovation gibt und einen Austausch bewährter Verfahren unter den EU-Mitgliedsstaaten fördert.

Während der Preiswettbewerb auf patentabgelaufenen Märkten gefördert wird, findet ein therapeutischer Wettbewerb auf patentgeschützten Märkten statt. Dieser Wettbewerb basiert in steigendem Maße auf zusätzlichen pharmako-ökonomischen Bewertungen, um den zusätzlichen medizinischen Nutzen von diesen neuen Arzneimitteln zu bestimmen. Jedoch sind diese innovativen Arzneimittel, deren Effizienz aufgrund der existierenden Unsicherheiten schwierig zu bewerten sind, kostspielig. Deswegen wird untersucht, inwiefern solche Vereinbarungen zu Risikoteilung ein Instrument darstellen können, um Informationsasymmetrien, insbesondere im Bereich adverser Selektion und des moralischen Risikos, zu lösen.

2. Ökonomische Analyse der Marktabgrenzung auf Pharmamärkten in der Europäischen Union: eine Anleitung

In dem zweiten Teil dieser Dissertation wird das Problem von den Substitutionskriterien angesprochen werden. Zu diesem Zweck wird die Definition der relevanten Marktabgrenzung auf Pharmamärkten untersucht. Hierbei wird insbesondere die Praxis der Europäischen Kommission zur Marktabgrenzung im Bereich Fusionen untersucht.

Im ersten Abschnitt wird der Begriff des relevanten Produktmarkts definiert, der die verschiedenen Marktteilnehmer bei einer Fusion (Verordnung (EG) n° 134/2004) oder einem angeblichen Missbrauch einer dominanten Position (Artikel 102 EG-Vertrag) identifiziert. Danach werden die Logik und die Grundprinzipien des relevanten Markts erklärt.

Der zweite Abschnitt beschäftigt sich mit der Praxis der Europäischen Kommission im Bereich Marktabgrenzung auf Pharmamärkten und mit der Anwendung des "hypothetischen Monopoltests". Die Anal-

ysen der Europäischen Kommission, deren Untersuchungen auf der ATC-Klassifizierung beruhen, um die Substitutionsniveaus (therapeutisch, chemisch oder molekular) zu definieren, berücksichtigen auch andere Kriterien je nach den Besonderheiten der betroffenen Arzneimittel. Solche Kriterien sind zum Beispiel die Hauptverwendung des Produktes. Allgemein können drei Kriterien unterschieden werden, die für die Europäische Kommission bei der Entscheidung zur Marktabgrenzung eine Rolle spielen. Das erste Kriterium sind die Wettbewerbsbedingungen, unter denen ein Produkt auf den Markt kommt, also ob das Produkt durch ein Patent geschützt ist oder nicht. Aufgrund der Bioäquivalenz der Generika werden sie in der Marktabgrenzung im selben Markt wie ihr Referenzarzneimittel betrachtet. Das zweite Kriterium ist, ob das Produkt für den Patienten verschreibungspflichtig ist oder nicht. Dieser Unterschied ist wichtig, weil die Arzneimittel, die nicht verschreibungspflichtig sind, in der Regel eine geringere Dosierung als die verschreibungspflichtigen Medikamente haben. Auch wenn sie den selben Wirkstoff beinhalten, können die verschreibungspflichtigen Versionen und die rezeptfreien Versionen des selben Arzneimittels zu einem anderen relevanten Markt gehören. Umgekehrt können zwei verschreibungspflichtige Arzneimittel zu zwei verschiedenen relevanten Märkten gehören, aber in ihrer rezeptfreien Version im selben relevanten Markt sein, weil die Dosierung niedriger ist. Das dritte Kriterium unterscheidet nach den besonderen Vertriebsmerkmalen der betroffenen Arzneimittel, also ob das Produkt entweder in der Apotheke oder im Krankenhaus vertrieben wird. Die Preisfestsetzungs- und Erstattungsmechanismen für diese beiden Vertriebswege sowie die Dosierungsform zur Darreichung sind oft in den einzelnen Mitgliedstaaten sehr unterschiedlich. Arzneimittel, die im stationären Bereich angewendet werden, passen sich der Situation der bettlägerigen Patienten an und werden meistens in injizierbarer Form verabreicht.

Schließlich führt der dritte und letzte Abschnitt des zweiten Kapitels eine ökonometrische Analyse der Fusionsentscheidungen der Europäischen Kommission zur Marktabgrenzung in der Pharmaindustrie in den Jahren 1989 bis 2011 durch. Die empirische Studie untersucht 217 relevante Märkte mit verschiedenen Logit- und Ordered-Logit-Modellen. Ziel der Studie ist es, einerseits die Kriterien zu identifizieren, auf Basis derer die Kommission ihre Entscheidungen trifft, um den relevanten Markt abzugrenzen, und anderseits auch die spezifischen Kriterien einzuordnen, die ab 2004, als die neue Verordnung in Kraft getreten ist, benutzt werden, um in der Zeit einen engeren Produktmarkt zu begrenzen.

In Übereinstimmung mit den Leitlinien zur relevanten Marktabgrenzung finden wir in der ersten Teilstichprobe 1989-2004, dass die Substitution auf der Nachfrageseite die Grundlage der relevanten Marktabgrenzung ist. Die Substitution auf der Angebotsseite spielt eine untergeordnete Rolle und ein Einfluss des politischen Umfelds kann nicht nachgewiesen werden. Einige besondere Kriterien führen zu speziellen Verschreibungspraktiken. Dies ist der Fall mit dem Verwendungszweck, dem Vertriebszweck, der Existenz neuer Wirkstoffe und dem Verkauf rezeptfreier Arzneimittel, die zu einer Abweichung von der üblichen

Analyse auf der therapeutischen Ebene (ATC 3) beitragen und dadurch den Umfang des relevanten Markts verringern.

Die anschließend durchgeführte Analyse der zweiten Teilstichprobe 2004-2011 kommt zum gleichen Ergebnis, was die Bedeutung des Substitutionsschemas auf der Nachfrageseite betrifft. Insbesondere zeigt die ökonometrische Analyse, dass die Produktnutzung und die Effizienzunterschiede unter den verschiedenen Produkten die Hauptkriterien sind, um den relevanten Marktumfang zu ATC 4 zu verringern. Hingegen sind der Wirkstoff, der Vertriebsweg und die Darreichungsform die Hauptkriterien, die zu einer engen Marktabgrenzung auf der Wirkstoffebene (ATC 5) führen. Die Studie führt zu denselben Ergebnissen für die rezeptfreien Arzneimittel aufgrund der Besonderheiten der ATC-Klassifikation.

3. Referenzpreissystem und seine Auswirkungen auf Innovationsanreize

Der dritte Teil dieser Dissertation untersucht die Funktion sowie die Auswirkungen eines internen Referenzpreissystems auf die Innovationsanreize von Pharmaunternehmen. Zu diesem Zweck werden zunächst die existierenden Verzerrungen im Wettbewerb zwischen Originalpräparaten und Generika betrachtet. Daraufhin sollen die Auswirkungen der Implementierung eines Referenzpreissystems erläutert werden. Die abschließenden Schlussfolgerungen unterstreichen die Relevanz eines solchen Systems, um Anreize für Innovationen zu setzen.

Zu Beginn des zweiten Teils wird das Konzept eines Referenzpreissystems definiert, wobei die verschiedenen Strukturen, welche in den einzelnen EU-Mitgliedstaaten Verwendung finden, skizziert werden. Insbesondere werden die in Deutschland und Frankreich angewendeten Systeme erklärt. Unabhängig von den jeweiligen Besonderheiten ist ein interner Referenzpreis für den Preis definiert, der zurückerstattet wird. Über diesen Preis hinaus bezahlt der Patient den vollen Preis von dem gewählten, speziellen Arzneimittel.

Im weiteren Verlauf der Arbeit werden die verschiedenen theoretischen (Zweifel and Crivelli, 1996; Merino-Castello, 2003; Brekke et al., 2007 und 2011; Bardey et al., 2011) als auch empirischen Modelle (Giuliani, 1998; Aronsson, 2001; Pavcnik, 2002, Grootendorst, 2002; Stargadt, 2010) zu Referenzpreissystemen in der ökonomischen Literatur beschrieben. Neben den Vorteilen der einzelnen Modelle werden auch die Grenzen dieser aufgezeigt. Hierbei wird vor allem deutlich, dass sich die bestehende empirische Literatur mit dem Informationsvorteil auseinandersetzt, welcher sich für die Originalpräparate im Vergleich zu Generika ergibt. Diese Informationsvorteile sind vor allem Werbestrategien für Originalpräparate,

die der Hersteller des Originalpräparats während des Patentschutzes durchgeführt hat. Diese haben das Ziel, nach Ablauf des Patentes die Loyalität der verschreibenden Ärzte und der Patienten gegenüber den Originalpräparaten zu fördern. In diesen Informationsvorteilen begründet sich die Verzerrung im Wettbewerb zwischen Originalpräparaten und Generika. Trotz der vorhandenen empirischen Literatur, welche diese Informationsvorteile beschreiben (Hurwitz and Case, 1988; Rizzo, 1999; Morton, 2000), geht die theoretische Literatur nicht im Detail auf diesen Aspekt ein (Hellerstein, 1998; Cabrales, 2003; Königbauer, 2007).

Aufbauend auf diese Erkenntnisse wird im Anschluss an den Literaturüberblick ein eigenes Modell vorgestellt, das die Auswirkung der Einführung eines Referenzpreises zeigt. Durch eine erhöhte Nachfrageelastizität zeigt sich, dass die von dem Informationsvorteil verursachten Verzerrungen durch den Referenzpreis ausgeglichen werden können.

Während die existierenden ökonomischen Modelle den Schwerpunkt auf die Auswirkungen des Referenzpreises auf Arzneimittelpreise und die Gesundheit der Patienten legen, konzentriert sich das präsentierte Modell zudem auf die Innovationsanreize für Pharmaunternehmen. Diese Erweiterung wird durch die Modellierung von Interaktionen zwischen dem Referenzpreis und den Innovationsanreizen ermöglicht. Basierend auf die Modelle von Ganuza et al. (2007, 2009) wird eine Annahme hinzugefügt, die eine Veränderung des Innovationsniveaus des Originalpräparats widerspiegelt. Somit kann gezeigt werden, dass die Auswirkungen des Referenzpreises auf das von den Pharmafirmen ausgewählte Innovationsniveau stark von dem ursprünglichen Investitionsniveau abhängt. Nur in dem Spezialfall, in dem das von den Pharmafirmen ausgewählte Innovationsniveau höher ist als das sozial optimale Innovationsniveau, ist die Implementierung eines Referenzpreissystems empfohlen. Es kann zudem gezeigt werden, dass die Effizienz dieser Maßnahme durch andere Strategien verstärkt werden kann. Die Verminderung der Heterogenität der verschreibenden Ärzte, welche sich loyal gegenüber dem Originalprodukt verhalten, und die Verringerung der Auswirkungen von Werbung können die Effizienz steigern.

Abschließend wird das präsentierte Modell mit den realen Maßnahmen und Auswirkungen in Deutschland und Frankreich gegenübergestellt. Die Implementierung der Referenzpreissysteme in beiden Ländern ist zwar unterschiedlich, aber von Maßnahmen begleitet, die die Loyalität zu Originalpräparaten senken und die Werbung regulieren.

4. Ökonomische Analyse von Vereinbarungen zur Risikoteilung auf Pharmamärkten

Nach der Analyse des Referenzpreissystems für Produkte, die nicht mehr unter Patentschutz stehen, bezieht sich der vierte und letzte Teil dieser Dissertation auf die Vereinbarungen zur Risikoteilung.

Mit den erhöhten Anforderungen für die Rückerstattung von Arzneimitteln und mit der zunehmenden Bedeutung der gesundheitsökonomischen Untersuchungen ist der Zugang zu Erstattung für innovative und teure Produkte deutlich erschwert. In diesen gesundheitsökonomischen Untersuchungen wird das Kosten-Nutzen-Verhältnis des neuen Arzneimittels berechnet. Jedoch wurde eine Differenzierung, beim von der Europäischen Kommission organisierten High Level Pharmaceutical Forum in 2005, gemacht. Die Effizienz eines Produktes ("effectiveness") bezüglich der tatsächlich erzielten Wirkungen des Arzneimittels sind von der Wirksamkeit ("efficacy"), die während der klinischen Studien bewertet wird, zu unterscheiden. Diese Wirksamkeit wird anhand von Patienten beurteilt, die durch bestimmte Kriterien für die klinische Studie ausgewählt wurden. Deswegen weicht die Effizienz eines Produktes von ihrer ursprünglichen beurteilten Wirksamkeit ab und liegt in der Regel unterhalb dieses Wertes. Wegen dieser Unsicherheit können die Krankenkassen und die pharmazeutischen Unternehmen Vereinbarungen zur Risikoteilung unterschreiben. In solchen Vereinbarungen, deren Modalitäten vielfältig sind, gewährleistet das Pharmaunternehmen die Effizienz seines Produktes und dafür wird es erstattet.

Nachdem die Umsetzung solcher Vereinbarungen in Deutschland, Frankreich, Italien und Großbritannien ausführlich dargestellt und untersucht wird, wird die theoretische Literatur untersucht (Lilico, 2003; Zaric et al. 2003, 2009; Capri et al, 2011; Barros, 2011; Antonanzas et al. 2011). Im weiteren Verlauf der Arbeit werden Vereinbarungen zur Risikoteilung theoretisch in Bezug auf Fragestellungen zu moralischem Risiko und adverser Selektion analysiert, was in der Literatur bisher nicht ausführlich gemacht wurde.

Was zunächst das moralische Risiko betrifft, entsteht es durch die Entkopplung von Effizienz und Wirksamkeit eines Produktes. Nach der Marktzulassung gibt das Preisfestsetzungsverfahren auf den Pharmamärkten den Unternehmen keinen Anreiz im Laufe des Lebenszyklus eines Arzneimittels zu investieren, um die Innovationen zu fördern und die Erfolgswahrscheinlichkeiten des Produktes zu erhöhen. So wird in einem Modell ohne und mit Informationsasymmetrien untersucht, inwiefern für den Nutzen der Krankenkasse und die Wohlfahrt der Gesellschaft Vereinbarungen zur Risikoteilung wünschenswert sind, weil sie Firmen Anreize geben, im Laufe des Lebenszyklus eines Arzneimittels zu investieren.

Im Bereich adverser Selektion wird in einem Signalisierungsmodell analysiert, inwiefern Vereinbarungen zur Risikoteilung die Informationsasymmetrien der Krankenkassen bezüglich der Effizienz eines Produktes

gegenüber den Pharmafirmen lösen können. In einem Modellrahmen, in dem die Firma die Initiative hat, entweder einen Standardvertrag oder eine Vereinbarung zur Risikoteilung zu schließen, kann gezeigt werden, dass nur eine Firma mit einem effizienten Produkt eine Vereinbarung zur Risikoteilung anbieten würde.

5. Schlussbemerkungen

Bei der ökonometrischen Analyse der relevanten Marktabgrenzung in EU-Fusionsentscheidungen von 1989 bis 2011 wurde eine Segmentierung zwischen innovativen Arzneimitteln, die auf therapeutischer Ebene im Wettbewerb stehen, und patentabgelaufenen Arzneimitteln, die in Preiswettbewerb zueinander treten, festgestellt. Dieses Ergebnis entspricht den fragmentierten Preis-und Erstattungsentscheidungen zwischen patentgeschützten und patentabgelaufenen Arzneimitteln. Trotz der verschiedenen Praktiken unter den Mitgliedsstaaten wird diese zweigleisige Politik benutzt, wobei eine Gesundheitstechnologiefolgenabschätzung und die damit verbundenen Maßnahmen wie Risikoteilung als ersten Schritt betrachtet werden. Diese Instrumente werden von komplementären Maßnahmen auf patentabgelaufenen Märkten, wie z.B. dem Festbetrag, ergänzt, um den Zielvorgaben näher zu kommen, wie es mit der Förderung von Innovationsanreizen oder der Lösung von Informationsasymmetrien der Fall ist. Unsere Analyse hat die Interdependenz beider Märkten gezeigt und den Bedarf hervorgehoben, eine globale politische Regulierungsstrategie der Mitgliedstaaten zu entwickeln und dabei die Bedeutung der gesamten Wertschöpfungskette mit den Großhändlern, den Apothekern und den Ärzten zu berücksichtigen.

Weitere Forschungsaspekte betreffen biologische Präparate. Solche Präparate, die eine zunehmende Bedeutung in den pharmazeutischen Märkten einnehmen, unterscheiden sich in ihren Eigenschaften von chemischen Arzneimitteln und, aufgrund der besonderen Wettbewerbssituation, erfordern sie eine spezifische öffentliche Regulierung.

Chapter 1

INTRODUCTION TO PHARMACEUTICAL MARKETS

ABSTRACT OF CHAPTER 1

Public regulation in pharmaceutical markets is distinct due to the characteristics of the demand, as well as the price-setting and reimbursement mechanisms which lead to the creation of two markets with different competition schemes. The first market, which contains patent-protected products, is characterised by therapeutic competition. The second type is an off-patent market, in which the entry of generic versions leads to price competition which is promoted by various cost-containment measures.

Consequently, the issues at stake in these markets differ. In patent-protected markets, the increasing use of pharmacoeconomic studies and the uncertainties over the effectiveness of new products, represent a barrier to reimbursement. In off-patent markets, barriers to entry include the informational advantage of off-patent originators over generic versions.

Based on these facts, three questions are raised, which will be answered by the thesis: How to define substitution patterns within pharmaceutical markets? How to promote price-competition in off-patent markets while giving innovation incentives to pharmaceutical firms? How to supply patients with innovative medicinal products while preserving healthcare budgets?

The aim of this first chapter is to introduce to regulation in pharmaceutical markets and present the three related questions which will be answered in the following chapters. To that purpose, in a first section, the characteristics of regulation in pharmaceutical markets will be presented (1.1). A second section will present some actual challenges in these markets (1.2). Finally, the third section will ask three questions dealing with the interactions between regulation and innovation incentives which will be answered along the following chapters (1.3).

1.1 Regulation and competition in pharmaceutical markets: a state of play

> "Are pharmaceutical markets fundamentally different from other markets? Who is the customer? Does price matter? Should a single drug define the market? Should generic drugs be in the same market as pioneer drugs or a distinct product market? " (Morse, 2003. p.635)

Once the characteristics of the demand and the importance of regulation have been reviewed in a first subsection (1.1.1), price setting mechanisms are analysed (1.1.2). Finally, features of competition patterns in off-patent and patent-protected markets are investigated (1.1.3).

1.1.1 Characteristics of the demand and importance of regulation

The characteristics of the pharmaceutical sector come from the different stakeholders involved and the institutional features in place. These elements can be divided between demand-side and supply-side specifics. Demand-side specifics concern the role and the interactions between the different stakeholders, prescribing physicians (1.1.1.1), pharmacies (1.1.1.2), health insurers and patients (1.1.1.3). Some agency issues take place as patients' access to medical treatment and medicines in the outpatient sector is regulated by doctors' prescriptions and pharmacists' dispensing.

1.1.1.1 Prescribing physicians and the implementation of financial incentives - Examples from Germany and France

An agency relation exists between the physician and the patient, in the sense that the physician knows more than their patient about their health conditions and their prospect of treatment. Thus, the usual demand-curve based on price-taking consumers does not give an exact picture of the pharmaceutical market. Prescribing physicians decide on the quantity of medical treatments and medicines. (Mc Guire, in Culyer, 2000, p.527).

Beyond the fixed institutional framework, the objective of recent stringent regulations in the EU and in general in OECD countries is to contain health expenses by acting on the demand-side, thus having an impact on the demand-substitution patterns. These measures target prescribing physicians, pharmacists and patients.

On the matter of physicians´ prescriptions, diverse measures such as providing target prescribing, or prescribing patterns, aim to offer them incentives to prescribe fewer costly medicines and more generic medicines. Generics are chemically identical copies of an out of patent reference product and are priced cheaper. In most of the EU member states, physicians have to prescribe a drug, when possible, using the International Non proprietary Name (so-called "INN"), corresponding to the active ingredient. This means that generic versions have the same INN as their originator drug.

Measures targeting prescribing physicians range from financial incentives to non-financial incentives, such as the release of prescribing guidelines. Financial measures can take various forms, such as in Germany the allocation of a physician budget,[1] or in France the implementation of special contracts to improve physicians´ individual practices ("Contrats d´amélioration des pratiques individuelles", hereinafter CAPI)[2].

In Germany, the physician´s budget takes the form of a "performance audit" (so-called "Wirtschaftlichkeitsprüfung"). Physicians will be audited if their performance is conspicuous, or if they belong to the 2% of physicians due to be audited each semester. The auditors look at invoiced volumes, as well as transfers, admissions to hospital, certificates of incapacity for work. The purpose of the performance audit is to avoid public health insurance expenses from getting out of control,[3] and in thus placing the responsability on the prescribing physicians.

In France, physicians who have subscribed to a CAPI commit, in exchange for financial compensation, to actively participate in prevention campaigns, improving the quality of healthcare for patients suffering from diabetes or high blood pressure, as well as promoting cheaper medicines. Their remuneration depends on the achievement of different goals in relation to their starting situations.

[1] Cf. SGB V, para.106.

[2] Cf. UNCAM Decision of 9 March http://www.legifrance.gouv.fr/affich Texte.do?cidTexte=JORFTEXT000020534299, last accessed March 2012.

[3] Paragraph 12 of the SGB V provide that " services must be sufficient, appropriate and affordable in economic terms (...) Services that are not necessary or wasteful cannot be claimed by patients, are not allowed to be achieved by service providers and to be approved by health insurance funds" (German source translated).

1.1.1.2 Pharmacists and measures restricting their choices - Examples from Germany and France

Medicines are not open-access, instead they are delivered by pharmacists who have a duty to provide the product mentioned on the prescription. If the prescription just mentions the INN, which is the case for pharmaceutical products which are not protected by a patent anymore, the pharmacist is responsible for offering the active ingredient corresponding to the prescription.

Various measures ensure that they dispense the cheapest product through the implementation of generic substitution and control their remuneration, or the discounts they are granted. Generic substitution implies that, if a physician prescribes according to the brand name of a product, the pharmacist has to dispense the generic version, which has the same chemical composition, in the same dosage, and is cheaper[4]. The choice of generic version is left to the pharmacist. This choice can however be constrained by legislation.

For example, in Germany, since April 2007[5] health insurers are entitled to sign a contract (so-called rebate contract, "Rabattvertrag") with pharmaceutical manufacturers for the supply of certain out of patent molecules (and sometimes also in-patent), so that their insurees can obtain products from the pharmaceutical manufacturer their health insurance signed a rebate contract with, and be reimbursed the maximum amount negotiated. Substitution criteria defined in the rebate contract include the same active ingredient, dosage, package size, and indication.

1.1.1.3 The role of health insurers and moral hazard issues

Though the patient consumes the pharmaceutical, they do not bear the full costs, instead insurance funds are the final payers. Health insurance may be state-based, private, or a combination of both.

The reimbursement of pharmaceuticals by health insurers leads the patients' demand to be relatively price-inelastic. Health insurance reimburses fully or only a part of the health expenses, which creates a moral hazard, as an asymmetry of information exists between the health insurer and the patient with regard to the patients' health status and their medicinal needs.

Patients are frequently required to pay a copayment which is either a fixed amount or a percentage of the price of the medicinal product. Measures which impact patients' reimbursement are also implemented to alleviate moral hazard issues which are inherent to health insurance. These different measures which affect all of the parties involved are widely used in EU member states.

[4] When the physician indicates that for a precise reason (intolerance, side-effects...), only the brand-name medicine is to be delivered, the pharmacist delivers the brand-name product.

[5] Cf. Section130a from the SGB V.

The Court of Justice of the European Union (hereinafter CJEU) refused the arguments brought by the Association of the British Pharmaceutical Industry (hereinafter ABPI) who asserted that the financial incentives schemes given to physicians were incompatible with the EU directive on medicinal products for human use (Directive 2001/83/EC)[6]. The CJEU found that while the directive prohibits promotional practices which may introduce a bias in medical prescribing, health authorities in the UK are qualified to decide on public policies and rationalise their pharmaceutical expenses provided the financial incentives given to the physician are based on objective criteria and the therapeutic evaluation of medicines is regular and published.

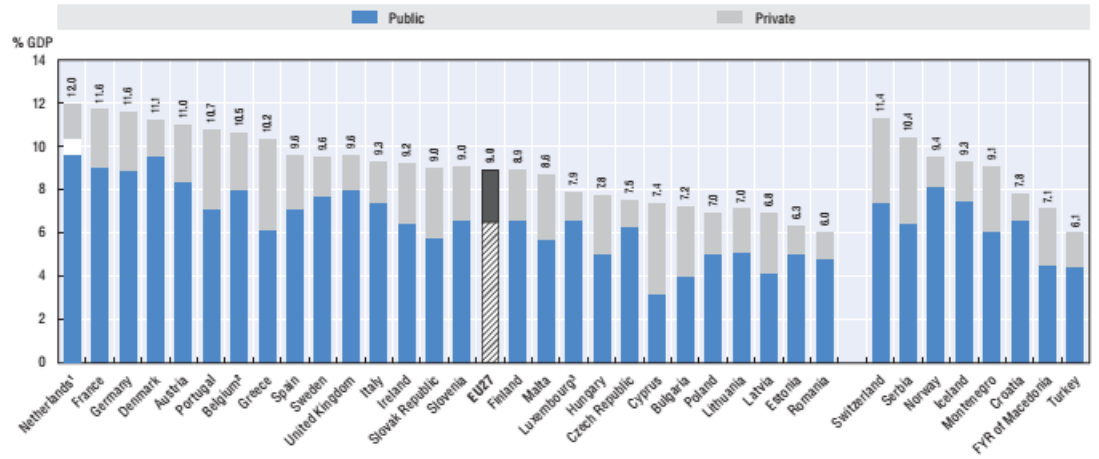
1.1.2 Prices and regulation

Supply-side specificity of pharmaceutical markets concerns the pricing and reimbursement of pharmaceuticals which are constrained by national regulation (1.1.2.1) and by cost-containment measures (1.1.2.2).

1.1.2.1 Pricing of pharmaceuticals and new pricing schemes

Pricing and reimbursement are a national responsability of member states. Pharmaceuticals are heavily regulated on an EU and national level. Pharmaceutical expenses are a key issue for decision-makers as they are the third biggest and most identifiable component of health expenses in the OECD countries after hospital and ambulatory care spending (EC, 2009).

Figure 1.1: Total health expenditure as a share of GDP (2010)



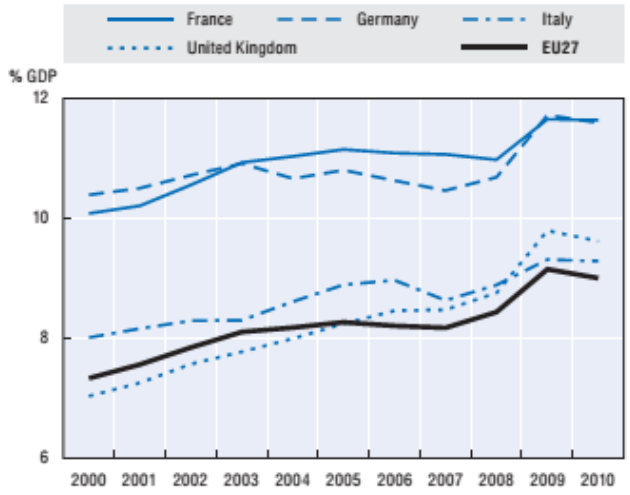
1. In the Netherlands, it is not possible to clearly distinguish the public and private share related to investments.
2. Public and private expenditures are current expenditures (excluding investments).
3. Health expenditure is for the insured population rather than resident population.

Source: OECD Health Data 2012; Eurostat Statistics Database; WHO Global Health Expenditure Database.

StatLink http://dx.doi.org/10.1787/888932705463

[6]Cf. case C-62/09,http://curia.europa.eu/jurisp/cgi-bin/form.pl?lang=FR&Submit=rechercher&numaff=C-62/09, last accessed October 2011.

Figure 1.2: Total health expenditure in selected EU member states (as a share of GDP, 2000-2010)



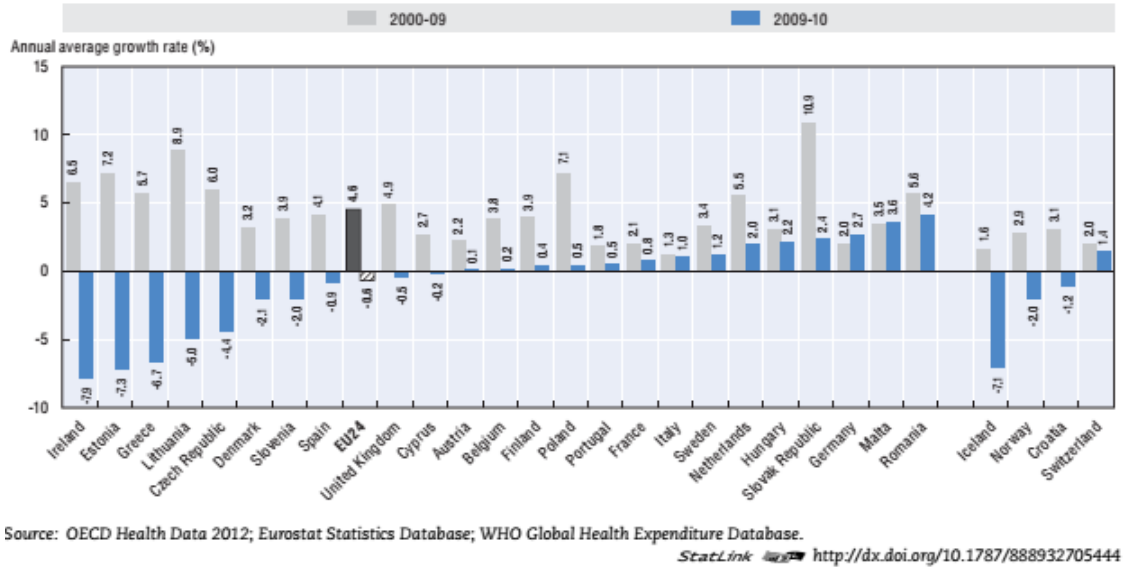
Source: OECD Health Data 2012; Eurostat Statistics Database; WHO Global Health Expenditure Database.

StatLink http://dx.doi.org/10.1787/888932705501

Healthcare costs are rising mainly due to the population ageing and the costs of new technologies. The average ratio of health spending to GDP in France, for example, which is ranked second in terms of healthcare spending, after the US, was around 11.2% in 2008, whilst in Germany it was 10.5% (OECD Health Data 2010). Total expenditure on pharmaceuticals represented around 17% of health expenditures in 2008 in France and 15.1% in Germany. While the manufacturer´s price excluding VAT of reimbursed pharmaceuticals sold in pharmacies fell by 0.85% and the public price by 0.86% due to price cuts (European Federation of Pharmaceutical Industries and Associations, hereinafter EFPIA, 2010, p.16). Figures 1.1, 1.2 and 1.3 provide an overview of some key figures in health expenditure during the period between 2000 and 2010.

With the exception of Denmark and Malta, price controls exist in EU member states. Pricing at the manufacturering level depends on the countries studied. The most common instrument is statutory pricing, which consists of setting prices based on a regulatory basis. Another possibility consists of a negotiated price between healthcare insurance and the pharmaceutical company, as is the case in France. In Germany, until recently, pharmaceutical manufacturers were free to set their prices. In France, medicinal products are priced according to negotiations between pharmaceutical manufacturers and health authorities, and often based upon medico-economic studies which assess the additional medical benefit of the drug. This price-fixing decision considers the medicine's market in a comprehensive way, by taking into account the direct and indirect consequences of the medicinal product´s cost according to price structures within a single and different therapeutic groups, and the economic consequences associated with

Figure 1.3: Annual average growth rate in healthcare expenditure per capita (in real terms, 2000-2010)



reimbursement for health insurance funds.

Public procurement is also widely used for hospital medicines and in some pharmacy markets, such as in Germany, in the case of rebate contracts between health insurance and pharmaceutical firms.

1.1.2.2 Price setting methods and cost-containment measures

Pricing and reimbursement decisions Pricing and reimbursement decisions for medicinal products are taken at a national level as it is the prerogative of each member state to be responsible for the organisation and delivery of health services and medical care[7]. Thus, the national healthcare authorities are free to set the prices of medicinal products and the treatments they are willing to reimburse with public health insurance. The objective of the Council Directive 89/105/EEC[8], so-called "Transparency Directive", is to ensure that national pricing and reimbursement systems are made in a transparent way and do not impede the EU-wide internal market. After the delivery of the marketing authorisation - whose purpose is to ensure quality, safety and efficacy of medicinal products either at a national or centralised level by the European Medicines Agency (hereinafter EMA) - each member state is in charge of price-setting and reimbursement, in compliance with the common procedural rules of the Transparency Directive.

Following the changes which occurred in the pricing and reimbursement landscape since 1989 and

[7] Cf. art.152(5) of the EEC Treaty available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:12002E152:EN:HTML, last accessed March 2013.

[8] Available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31989L0105:en:HTML, last accessed July 2013.

the Court of Justice case law, which ruled that all national measures to control the prices of medicinal products or to restrict the range of medicinal products, must comply with the Directive[9], the European Commission (hereinafter EC) proposed to revise the Transparency Directive. The EC´s main concern was the potential distortions which were stressed by the Commission report on the pharmaceutical sector in 2009 (hereinafter Pharmaceutical Sector Inquiry)[10] of the internal market due to the increasing national measures taken to control public health expenditure. For this reason, the EC´s initial proposal for revision was providing a faster access to medicinal products through the guarantee of shorter time limits for national, regional, or local decisions on pricing and reimbursement of all medicinal products (120 days instead of 180 days as a general rule) and generic medicinal products in particular (30 days instead of 180 days) when the price of the reference product had already been approved, or when it had already been included in the public health insurance system, as well as clarification concerning innovative pricing and reimbursement procedures.

Cost-containment measures Various cost-containment measures influence price setting. Price-setting evolves with the increase of more stringent governmental regulation applied to pharmaceutical manufacturers and distributors across the EU. These measures concern price setting and reimbursement conditions with the objective of containing health expenses.

New institutions were also created in EU member states to weaken manufacturers´ power to maintain high prices and high reimbursement rates on patented drugs. These new institutions represent a powerful element of competition in the pricing and reimbursement of patented drugs.

With regards to the control of prices, price cuts are commonly used by governments to curb health expenses. Even in countries such as Germany where price-setting was previously unrestricted, pricing is now constrained. In 2011, the law on the Reorganisation of the Medicinal Products Market ("Arzneimittelmarkt-Neuordnungsgesetz" hereinafter AMNOG) reorganised the pricing and reimbursement schemes in Germany. It introduced a three-year price freeze and increased the rebate (so-called "Herstellerrabatt") in place for patent-protected drugs which is equal to 7% since 1 April 2014 until December 2017[11]. It also introduced price negotiation for patent-protected drugs between manufacturers and the Federal Joint Committee ("Gemeinsamer Bundesausschuss", hereinafter G-BA) from 1 January

[9]Cf. Case C-229/00 Commission of the European Communities v Republic of Finland [2003] ECR 5727, available at http://curia.europa.eu/juris/showPdf.jsf;jsessionid=9ea7d2dc30db8aa85cc6f54a4905b06a98f276fd95b2.e34KaxiLc3qMb40Rch0SaxqTc390?text=&docid=86051&pageIndex=0&doclang=EN&mode=req&dir=&occ=first&part=1&cid=355846, last accessed March 2012.

[10]Cf. Communication from the Commission "Executive Summary of the Pharmaceutical Sector Inquiry Report" (COM (2009)351 final) and the annexed Staff Working Document: "Report on the Pharmaceutical Sector Inquiry", available at http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/, last accessed August 2013.

[11]Cf. 14. SGB V- Änderungsgesetz of 21.02.2014, available at http://dipbt.bundestag.de/extrakt/ba/WP18/567/56764.html, last accessed June 2014.

2011 onwards. This measure aimed at providing greater leverage to the insurers and led to a decrease in drug prices. In France, the introduction in 2004 of the Regional Health Agencies[12] ("Agences Régionales de Santé", so-called ARS) resulted in greater purchasing power for hospitals.

In the EU, twenty-four member states also implemented a system called "External Reference Pricing", which consists of setting the price of a pharmaceutical on the basis of the price of a selection of identical and comparable products in other countries (Garcia Marinoso et al., 2011). The number of countries which are included in the basket range from three in Slovenia to twenty-six in Latvia and the Czech Republic. The price set may be the average price of the basket, the average of the lowest prices or even the lowest price which is regularly adjusted (EP, 2011, p. 36).

Price cuts and price controls are not the only leverage used by governments to curb health expenses on the supply side. Tendering procedures are widely used to supply hospital pharmaceutical markets and more recently also for pharmacy markets. Tendering can either take place between the pharmaceutical manufacturers and hospitals, or between the pharmaceutical manufacturers and health insurers. Tendering procedures enable health insurers and hospitals to partner and have more purchasing power, in order to decrease prices, such as in the framework of the rebate contracts ("Rabattverträge") in Germany.

Even if the price is set freely, or results from negotiations with health authorities, a control of direct expenditures is implemented by health authorities. Consequently, price-volume agreements are commonly used, for example in France where the final price paid to pharmaceutical companies depends on the quantities of the product sold. Price-volume agreements consist of fixing a price, based on a foreseen volume sold, with a pay-back clause if this volume turns out to be too high. Price cuts conform with EU law and member states are allowed to decrease pharmaceutical prices several times a year based on expense estimates[13]. Rate-of-return regulation is used in the UK within the framework of the "Pharmaceutical Price Regulation Scheme" (hereinafter PPRS) which acts as a mechanism for profit control. The PPRS is a voluntary agreement signed between the UK government and the industry, and targets manufacturers´ profits on sales to the National Health Service (hereinafter NHS). Beyond a certain threshold of profits, pharmaceutical manufacturers have to pay back the excess or reduce their prices (EP, 2011, p. 37). The current 2014 PPRS started on 1 January 2014 and runs for five years. The agreement specifies that the growth of sales for NHS-branded products will remain 0% for the next two years and will be limited to less than 2% for the three following years. The introduction of a value-based pricing system was initially proposed for new active substances starting from 1 January 2014. However, the current agreement specifies

[12]Cf. website of the Regional Health Agencies, http://www.ars.sante.fr/portail.0.html.

[13]Cf. CJCE, 2 April 2009, case C-352/07, A. Menarini Industrie Farmaceutiche riunite Srl e.a. / Ministero della salute et Agenzia Italiana del Farmaco, http://curia.europa.eu/fr/actu/communiques/cp09/aff/cp090030fr.pdf.

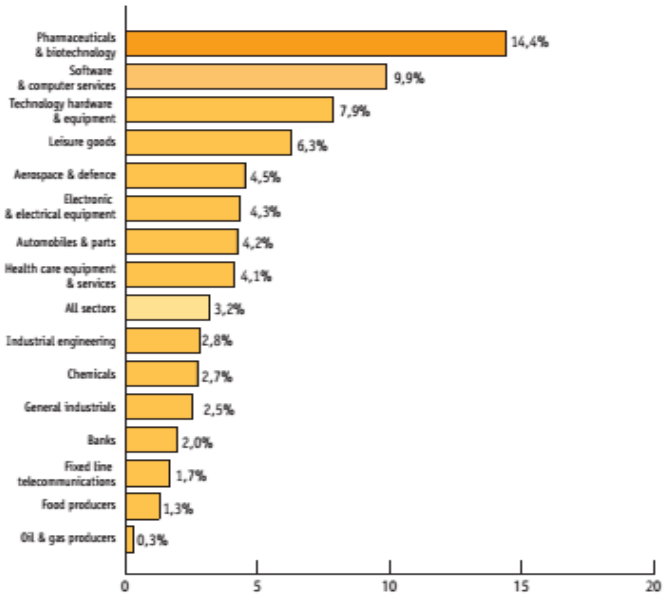
that companies may request value-based appraisal of their new medicines[14].

1.1.3 R&D and the innovation process in the pharmaceutical industry

The pharmaceutical sector is a research-intensive industry. In 2012, the R&D sales ratio in the pharmaceutical and biotechnology sector in the EU was 14.4%, far above the next highest industry investing the most in R&D which was the software and computers services industry at 9.9% (EFPIA, 2014).

Innovation and patent expiry lead to a continually competitive and changing environment. Competition in the pharmaceutical industry differs depending on the competition status of the product, meaning whether it is still protected by a patent (1.1.3.1) or not (1.1.3.2).

Figure 1.4: Ranking of industrial sectors by R&D/sales ratio (2012)



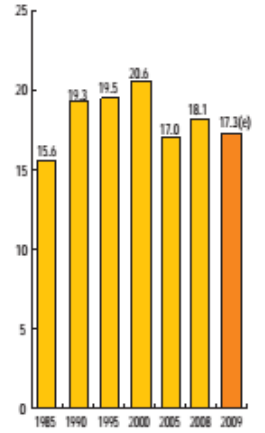
Sources: EFPIA, 2014

1.1.3.1 Therapeutic competition in on-patent markets and "follow-on" products

Issues around the innovation process Prior to being granted a marketing authorisation, new medicinal products have to pass three separate clinical trials, among others. Clinical trials correspond to:

[14] Cf. The Pharmaceutical Price Regulation Scheme 2014, p. 19, available at https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/282523/Pharmaceutical_Price_Regulation.pdf, last accessed June 2014.

Figure 1.5: R&D as a percentage of sales in the EU (1985-2009)



Source: EFPIA Member Associations (official figures)
(e): EFPIA estimate

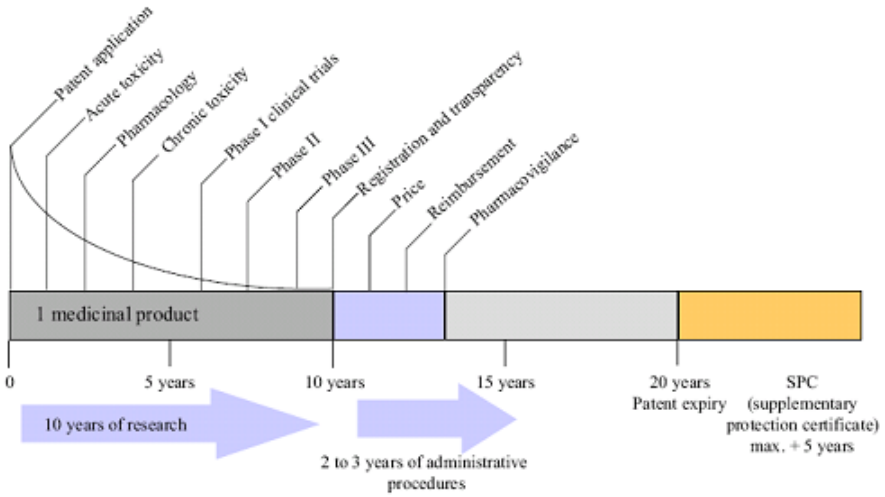
> "any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy." (Directive 2001/20/EC, art.2 (a).)

Phase I corresponds to the first testing phase on human beings. Its purpose is primarily to gain knowledge regarding the clinical effectiveness of the product and is, in general, performed on a small amount of healthy volunteers.

Phase II of clinical trials is performed with a larger amount of volunteers and patients, in order to study the efficacy and toxicity of the new drugs with regards to a certain pathology. The last clinical trial phase before marketing authorisation, phase III, concerns a large panel of patients and aims at gathering information on the product. Phase III of clinical trials is by far the most expensive and time-consuming phase. It corresponds to more than 35% of the R&D costs, while phases I and II together represent less than 25% (EFPIA, 2010). It is not rare for a marketing authorisation to be submitted to health regulatory authorities while the new medicinal product is still undergoing phase III clinical tests. Phase IV takes place post marketing and corresponds to the gathering of information on the medicine by comparing it to other therapeutic alternatives, assessing the long-term effects and the cost effectiveness of the medicinal product[15] Figure 1.6 summarises in a graph the medicinal product's life cycle.

[15] Cf. the website Orphanet, http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN&stapage=ST_EDUCATION_EDUCATION_ABOUTORPHANDRUGS_CLINICALTRIALS, last

Figure 1.6: Life cycle of a medicinal product



Sources: Ecorys, EC, 2009

A research intensive industry Developing a medicine is a long and costly process due to the complex nature of sciences and the clinical trials involved, especially in the third phase involving large numbers of patients. In 2012, the average costs of developing a new product was estimated at €1.5 billion (EFPIA, 2014). The patent system acts as an incentive for firms to invest in research for innovative products.

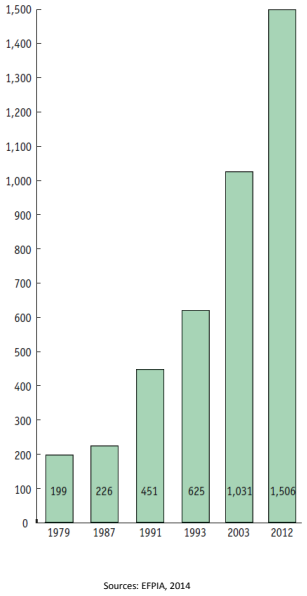
A patent is both a protection and a reward for an innovative medicine, an innovative molecule, or a formulation, giving the firm which owns it a temporary monopoly. During the patent's life, no one is allowed to copy the product or invent around it. Hence, the innovative drug's price can be set above production costs with a substantial margin. During patent life, the only competition possible is therapeutic competition, between medicines having the same indication, but based upon another molecule or formulation. The patent impedes an imitator from copying the medicine and pricing it lower as they do not have to undertake research and could market the product quickly. As a R&D intensive industry, the pharmaceutical industry is in a continuous process of innovation and imitation. The objective of this therapeutic competition at an early stage is to acquire market shares by pointing out new specific properties. However, during later stages, as a result of the marketing of generic versions, price competition takes place.

In the EU, pharmaceutical firms invested around €27 billion in R&D in 2010, which represents a growth rate of 4.4% in the period 2006-2010.

On average, one or two substances out of 10 000 passed the different stages to be marketed. It takes at least twelve years, often more, for an active substance after being synthesised for the first time to come to the market for an average development cost of more than €1 billion (EFPIA, 2010). It is estimated

accessed October 2011.

Figure 1.7: Estimated full costs of bringing a new chemical or biological to the market (in $ million, 2011)



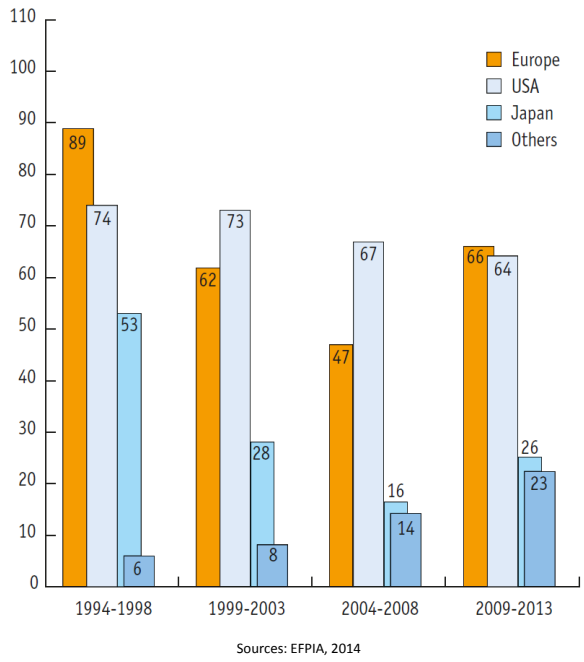
that only between one in 5,000 to one in 10,000 interesting molecular entities will eventually be further developed and eventually marketed by pharmaceutical companies (Ecorys Final Report, 2009). Figure 1.8 shows the number of NMEs brought to the market from 1994 to 2013.

Table 1.1: Overview of the clinical trial phases

STAGE	NUMBER AND TYPES OF PATIENTS	DURATION	PURPOSE
Phase I	20-100 healthy volunteers	Up to 1 year	To ensure the medicine is safe and find the most suitable dose
Phase II	Up to several hundred patients	1-2 years	To assess the effectiveness and look for side-effects
Phase III	Several hundred to several thousands patients	2-4 years	To confirm effectiveness and monitor any side-effects from long-term use
Phase IV	Several thousands patients	Variable	To develop new treatment uses, compare with other treatments, determine the clinical effectiveness and long-term safety of the medicine in a wide-variety of patient types and/or to satisfy conditions of authorisation

Source: EFPIA, 2010, p. 8

Figure 1.8: Number of NMEs launched worldwide (1994-2013)



The costs of discovering and developing a new molecule are high. It was estimated to be around $1318 million in 2006, which represents a considerable increase compared to $801 million in 2001. However, R&D costs differ significantly across therapeutic areas. While R&D costs for HIV/AIDS are around $540 million, they increase for cancer therapy up to $1042 million (ESMT White Paper, 2010, p. 20). The innovation process for pharmaceuticals can be divided into a discovery, and a development phase. Figure 1.9 shows that technical and clinical success probabilities vary greatly across the different indications and clinical phases. Taking Alzheimer´s disease, for example, the probabilities of success are 30.8% for phase I, 65.9% for phase II, and 36.4% for phase III of clinical trials. For anxiety disorders which is a particularly risky area, the probabilities of success are divided by around two and decrease respectively to 12.3%, 38.9% and 16.7% (ESMT White Paper, 2010, p.26).

Segmentation of R&D activities: "First-in-class" vs. "best-in-class" The sector inquiry on the pharmaceutical industry (DG COMP, 2009) - whose purpose was to investigate why fewer innovative drugs were brought to market and why the marketing of generic versions seemed to be delayed in the EU - describes R&D activities in the pharmaceutical industry as producing a continuum of innovation. It found two distinct categories of medicinal products depending on the degree of innovation of the medicinal product and the R&D costs involved. Innovation in the pharmaceutical industry is indeed diversified. This heterogeneity covers the essential differentiation between "first-in-class" and "best-in-class" medicinal products (DiMasi and Paquette, 2004). First-in-class products correspond to new medicinal products which are granted a period of exclusivity by means of a patent. First-in-class products may, or may not, correspond to best-in-class products. The latter are a consequence of incremental modifications made on the former. Thus, depending on the incremental modifications performed, best-in-class may, or may not, be protected by a patent. Figure 1.10 provides an overview of the average time to market entry for first-in-class and follow-on products in previous decades in the US (Di Masi, 2004).

The first category mentioned by the sector inquiry, which covers first-in-class products, consists of fundamental innovation leading to the discovery of new medicines containing new chemical substances (NCEs) and which requires significant investment without any guarantee of success. Consequently, a medicinal product that is the result of fundamental innovation only has imperfect substitutes in terms of efficacy, safety, and side-effects; the only competitors are therapeutic substitutes containing other active ingredients. Figure 1.11 shows 2014 sales forecasts for world's top selling prescription medicines. A medicinal product will be in a monopoly as long as no other therapeutic alternative exists (Scherer, 2000). Once a therapeutic alternative exists, products can be considered as imperfect substitutes, thus their cross-price terms are positive. During the product´s early stages, it is only in imperfect competition

Figure 1.9: Breakdown of success probabilities across clinical phases and indications/diseases

Indication/Disease	Prob. Phase-I Success	Prob. Phase-II Success	Prob. Phase-III Success
Alzheimer's disease	30.8%	65.9%	36.4%
Anxiety disorders	12.3%	38.9%	16.7%
Asthma	65.6%	37.6%	77.4%
Bacterial infections	62.4%	69.0%	89.1%
Cancer	61.9%	27.1%	82.4%
Cardiovascular disorders	58.2%	60.0%	75.0%
Chemoprotection	56.0%	60.0%	62.5%
Depression	35.2%	53.3%	47.5%
Diabetes mellitus	50.7%	57.2%	60.0%
Epilepsy	43.0%	58.9%	64.7%
Erectile dysfunction	80.0%	75.0%	80.0%
HIV-1 infections	53.5%	49.9%	62.5%
Hepatitis B	92.9%	79.1%	96.4%
Hypertension	59.9%	44.7%	81.0%
Malaria	81.7%	66.7%	100.0%
Migraine	59.5%	61.9%	71.4%
Parkinson's disease	61.1%	65.3%	70.0%
Psychotic disorders	39.6%	66.6%	50.0%
Thrombosis	45.5%	47.1%	64.3%
Transplant rejection	56.7%	56.9%	67.0%

Sources : ESMT, 2010

Figure 1.10: Examples of first-in-class and follow-on products (1960-1998)

Class	First in class	US approval date	Second entrant	US approval date	Time entry
K+ sparing diuretic	Aldactone® (spirinolactone)	01/02/1960	Dyrenium® (triamterene)	08/10/1964	4.6
benzodiazepine	Valium® (diazepam)	11/15/1963	Serax® (oxazepam)	06/04/1965	1.6
first generation quinolone	NegGram® (nalidixic acid)	03/06/1964	UtiBID® (oxolinic acid)	07/01/1975	11.3
bile acid sequestrant	Cuemid® (cholestyramine resin)	10/15/1964	Colestid® (colestipol)	04/04/1977	12.5
loop diuretic	Lasix® (furosemide)	07/01/1966	Edecrin® (ethacrynic acid)	01/10/1967	0.5
fibrate	Atromid-S® (clofibrate)	02/08/1967	Lopid® (gemfibrozil)	12/21/1981	14.9
benzimidazole (anthelmintic)	Mintezol® (thiabendazole)	04/07/1967	Vermox® (mebendazole)	06/28/1974	7.2
beta-antagonist	Inderal® (propranolol HCl)	11/13/1967	Lopressor® (metoprolol tartrate)	08/07/1978	10.7
pyrimidine nucleoside analogue	Cytosar® (cytarabine)	06/17/1969	FUDR® (floxuridine)	12/18/1970	1.5
first generation cephalosporin	Keflex® (cephalexin)	01/04/1971	Velosef® (cephradine)	08/05/1974	3.6
rifamycin antibiotic	Rifadin® (rifampin)	05/21/1971	Mycobutin® (rifabutin)	12/23/1992	21.6
retinoid (dermatologic)	Retin-A® (tretinoin)	10/20/1971	Accutane® (isotretinoin)	05/07/1982	10.6
beta-agonist	Alupent Syrup® (metaproterenol sulfate)	07/31/1973	Bricanyl® (terbutaline sulfate)	03/25/1974	0.7
anthracycline	Adriamycin® (doxorubicin)	08/07/1974	Cerubidine® (daunorubicin HCl)	12/19/1979	5.4
alpha-blocker	Minipress® (prazosin HCl)	06/23/1976	Hytrin® (terazosin HCl)	08/07/1987	11.1
H2-antagonist	Tagamet® (cimetidine)	08/16/1977	Zantac® (ranitidine)	06/09/1983	5.8
biphosphonate	Didronel® (etidronate disodium)	09/01/1977	Aredia IV® (pamidronate disodium)	10/31/1991	14.2
selective estrogen receptor modulator	Nolvadex® (tamoxifen)	12/30/1977	Fareston® (toremifene citrate)	05/29/1997	19.4
platinum anticancer	Platinol® (cisplatin)	12/19/1978	Paraplatin® (carboplatin)	03/03/1989	10.2
second generation cephalosporin	Ceclor® (cefaclor)	04/04/1979	Cefzil® (cefprozil monohydrate)	12/23/1991	12.7
ACE-inhibitor	Capoten® (captopril)	04/06/1981	Vasotec® (enalapril maleate)	12/24/1985	4.7
calcium channel blocker	Isoptin® (verapamil)	08/12/1981	Procardia® (nifedipine)	12/31/1981	0.4
guanine derivative	Zovirax® (acyclovir)	03/29/1982	Cytovene® (ganciclovir)	06/23/1989	7.2
insulin (rDNA)	Humulin® (insulin)	10/28/1982	Novolin R® (insulin)	06/25/1991	8.7
chromatin function inhibitor	VePesid® (etoposide)	11/10/1983	Vumon® (teniposide)	07/14/1992	8.7
LHRH-agonist	Lupron® (leuprolide acetate)	04/09/1985	Zoladex® (goserelin acetate)	12/29/1989	4.7
non-sedating antihistamine	Seldane® (terfenadine)	05/08/1985	Hismanal® (astemizole)	12/29/1988	3.6
cannabinoids for nausea	Marinol® (dronabinol)	05/31/1985	Cesamet® (nabilone)	12/26/1985	0.6
human growth hormone (rDNA)	Protropin® (somatrem)	10/17/1985	Humatrope® (somatropin)	03/08/1987	1.4
thienamycin	Primaxin® (imipenem/cilastatin) sodium	11/26/1985	Merrem I.V.® (meropenem)	06/21/1996	10.6
second generation quinolone	Noroxin® (norfloxacin)	10/31/1986	Cipro® (ciprofloxacin HCl)	10/22/1987	1.0
nucleoside reverse transcriptase inhibitor	Retrovir® (zidovudine)	03/19/1987	Videx® (didanosine)	10/09/1991	4.6
statin (HMG-CoA inhibitor)	Mevacor® (lovastatin)	08/31/1987	Pravachol® (pravastatin sodium)	10/31/1991	4.2
tissue plasminogen activator (rDNA)	Activase® (alteplase [TPA])	11/13/1987	Retavase® (reteplase)	10/30/1996	9.0
alpha-1 proteinase inhibitor	Prolastin® (alpha-1-proteinase inhibitor)	12/02/1987	Aralast® (alpha-1-proteinase inhibitor)	12/23/2002	15.1
selective serotonin reuptake inhibitor	Prozac® (fluoxetine HCl)	12/29/1987	Zoloft® (sertraline HCl)	12/30/1991	4.0
nonsteroidal anti-androgen	Eulexin® (flutamide)	01/27/1989	Proscar® (finasteride)	06/19/1992	3.4
third generation cephalosporin	Suprax® (cefixime)	04/28/1989	Vantin® (cefpodoxime proxetil)	08/07/1992	3.3
proton pump inhibitor	Prilosec® (omeprazole)	09/14/1989	Prevacid® (lansoprazole)	05/10/1995	5.7
synthetic triazole	Diflucan® (fluconazole)	01/29/1990	Sporanox® (itraconazole)	09/11/1992	2.6
surfactant	Exosurf Neonatal® (colfosceril palmitate)	08/02/1990	Survanta® (beractant)	07/01/1991	0.9
5HT3-antagonist	Zofran IV® (ondansetron HCl)	01/04/1991	Kytril® (granisetrron HCl)	12/29/1993	3.0
ADP-induced platelet aggregation inhibitor	Ticlid® (ticlopidine)	10/31/1991	Plavix® (clopidogrel bisulfate)	11/17/1997	6.1
extended spectrum macrolide	Biaxin® (clarithromycin)	10/31/1991	Zithromax® (azithromycin)	11/01/1991	0.0
Factor VIII (rDNA)	Recombinate® (rurioctocog alfa)	01/01/1992	Kogenate® (Factor VIII)	02/02/1993	1.1
triptan	Imitrex® (sumatriptan succinate)	12/28/1992	Zomig® (zolmitriptan)	11/25/1997	4.9
taxane	Taxol® (paclitaxel)	12/29/1992	Taxotere® (docetaxel)	05/14/1996	3.4
low-molecular-weight heparin	Lovenox® (enoxaparin)	03/29/1993	Fragmin® (dalteparin sodium)	12/22/1994	1.7
interferon	Betaseron® (interferon beta-1b)	07/23/1993	Avonex® (interferon beta-1a)	05/17/1996	2.8
cholinesterase inhibitor	Cognex® (tacrine)	09/09/1993	Aricept® (donepezil)	11/25/1996	3.2
H1-antagonists (ophthalmic)	Livostin® (levocabastine)	11/10/1993	Patanol® (olopatadine HCl)	12/18/1996	3.1
serotonin and norepinephrine reuptake inhibitor	Effexor® (venlafaxine HCl)	12/28/1993	Serzone® (nefazodone HCl)	12/22/1994	1.0
macrolide immunosuppressive	Prograf® (tacrolimus)	04/08/1994	Rapamune® (sirolimus)	09/15/1999	5.4
carbonic anhydrase inhibitor	Trusopt® (dorzolamide HCl)	12/09/1994	Azopt® (brinzolamide)	04/01/1998	3.3
nonpeptide angiotensin-receptor blocker	Cozaar® (losartan potassium)	04/14/1995	Diovan® (valsartan)	12/23/1996	1.7
prostacyclin	Flolan® (epoprostenol sodium)	09/20/1995	Remodulin® (treprostinil)	05/21/2002	6.7
protease inhibitor	Invirase® (saquinavir)	12/06/1995	Norvir® (ritonavir)	03/01/1996	0.2
aromatase inhibitor	Arimidex® (anastrozole)	12/27/1995	Femara® (letrozole)	07/25/1997	1.6
topoisomerase-1 inhibitor	Hycamtin® (topotecan HCl)	05/28/1996	Camptosar® (irinotecan HCl)	06/14/1996	0.1
prostaglandin analogue (ophthalmic)	Xalatan® (latanoprost)	06/05/1996	Rescula® (unoprostone isopropyl)	08/03/2000	4.2
non-nucleoside reverse transcriptase inhibitor	Viramune® (nevirapine)	06/21/1996	Rescriptor® (delavirdine mesylate)	04/04/1997	0.8
leukotriene	Accolate® (zafirlukast)	09/26/1996	Zyflo® (zileuton)	12/09/1996	0.2
third generation quinolone	Zagam® (sparfloxacin)	12/19/1996	Raxar® (grepafloxacin)	11/06/1997	0.9
thiazidolinedione	Rezulin/Prelay® (troglitazone)	01/29/1997	Avandia® (rosiglitazone)	05/25/1999	2.3
follitropin (rDNA)	Gonal-F® (follitropin alpha)	09/29/1997	Follistim® (follitropin beta)	09/29/1997	0.0
meglitinide	Prandin® (repaglinide)	12/22/1997	Starlix® (nateglinide)	12/22/2000	3.0
COMT inhibitor	Tasmar® (tolcapone)	01/29/1998	Comtan® (entacapone)	10/19/1999	1.7
hirudin-based thrombin inhibitor	Refludan® (lepirudin)	03/06/1998	Angiomax® (bivalirudin)	12/15/2000	2.8
cGMP-specific PDE5 inhibitor	Viagra® (sildenafil citrate)	03/27/1998	Levitra® (vardenafil)	08/19/2003	5.4
glycoprotein IIb/IIIa antagonist	Aggrastat® (tirofiban HCl)	05/14/1998	Integrilin® (eptifibatide)	05/18/1998	0.0
glucagon (rDNA)	GlucaGen® (glucagon)	06/22/1998	Glucagon® (glucagon)	09/11/1998	0.2
COX-2 inhibitor	Celebrex® (celecoxib)	12/31/1998	Vioxx® (rofecoxib)	05/20/1999	0.4

Figure 1.11: Sales forecasts for world's top 10 drugs in 2014

Sales forecasts for world's top 10 drugs in 2014		
1. Avastin (cancer)	Roche	$8.9 bln
2. Humira (arthritis)	Abbott	$8.5 bln
3. Enbrel (arthritis)	Pfizer/Amgen	$8.0 bln
4. Crestor (cholesterol)	AstraZeneca	$7.7 bln
5. Remicade (arthritis)	Merck/J&J	$7.6 bln
6. Rituxan (cancer)	Roche	$7.4 bln
7. Lantus (diabetes)	Sanofi-Aventis	$7.1 bln
8. Advair (asthma/COPD)	GlaxoSmithKline	$6.8 bln
9. Herceptin (cancer)	Roche	$6.4 bln
10.NovoLog (diabetes)	Novo Nordisk	$5.7 bln

Source: Thomson Reuters (2014)

with therapeutic substitutes having different active ingredients, which means different efficacy results, safety profiles, and side-effects. Market shares are acquired by stressing inequality and superiority of each product. Only very innovative firms can compete on therapeutic grounds. These firms change over time and vary depending on the therapeutic area concerned.

The second category, including best-in-class products, corresponds to incremental innovation resulting from the development of existing medicines (so-called "follow-on" or "me-toos" medicinal products) through the development of a new formulation, a new mode of delivery, or the combination of previously disclosed active substances, which requires less time and investment. Follow-on medicinal products offer little, if any, innovation and additional benefits in terms of compliance or administration, instead serving primarily to retain the revenue streams of the first generation product. Combe and Haug (2006a) explain the presence of me-toos drugs by the decreasing profitability of R&D and the increasing of competition and regulatory pressures, so that firms seek to optimise the life cycle of their product and expand their marketing well beyond the patent life. One example of a me-too product is Prilosec (omeprazole) from AstraZeneca which is a proton pump inhibitor drug (so-called "PPI") which decreases the amount of acid produced in the stomach. Another well-known me-too product is Nexium (esomeprazole), also from AstraZeneca. The difference between omeprazole and esomeprazole is the molecular configuration. In its molecular

configuration, Nexium is the left-handed version of omeprazole. AstraZeneca claimed that this left-handed configuration improved the efficacy of Nexium over Prilosec. The extent of Nexium's efficacy gains has been disputed. For example, the UK healthcare authority, the National Institute for Health and Clinical Excellence (hereinafter NICE) with respect to esomeprazole ascertained that:

> "there is currently no reason to use expensive PPI's in preference to any of the other PPI's available when compared at appropriate, equivalent doses. Furthermore, it is highlighted that the PPI's most recently marketed on the NHS (esomeprazole and rabeprazole) offer no advantage in clinical effectiveness over established PPI's, plus there is also less evidence of long-term safety". (NICE, 2012)[16]

Impact of follow-on products on competition in on-patent markets

According to the data of the Directorate General for Competition of the EC (DG COMP, 2009), 55.3% of the top selling products which have lost their exclusivity between 2000 and 2007 have second-generation products. As a consequence, it notes that second-generation products replace first-generation products and often constitute a bigger part of the firm's turn-over.

The impact of follow-on products on the competitive marketplace is disputed. Follow-on products are claimed to offer few benefit, compared to available alternatives, while having a considerable impact on public health finances. Di Masi et al. (2004) explain in their paper that follow-on products are beneficial for health insurers as they limit the exclusivity of the first-in-class medicinal product and decrease its price while improving the treatment of some patients who responded poorly to the first-in-class treatment. Another study by Jena et al. (2009) investigates the impact of marketing on follow-on products in five main medicinal classes between 1992 and 2004 in the US: statins, H-2 receptor antagonists (H2RAs), proton pump inhibitors (PPIs), angiotensin-converting-enzyme inhibitors (ACE inhibitors), and selective serotonin reuptake inhibitors (SSRIs). They argue that the impact of follow-on products depends mainly on physician's prescription behaviour and whether they consider follow-on products as close substitutes on the basis of their therapeutic benefits. As a result, they found that the prices of follow-on products are high because their clinical benefits are perceived by physicians as worth the additional costs. Their prescription can be explained by the low price-elasticity of demand as health insurers are the final payers. Thus, they concluded that follow-on products have an important impact in impeding price competition between medicinal products.

[16] Cf. Medicines Management Team Information for patients, Esomeprazole (Nexium ®)/ rabeprazole (Pariet ®) therapeutic switch, NICE, available at http://www.iow.nhs.uk/uploads/MedManagement/pdfs/Esomeprazole_and_rabeprazole_to_generic_PPI.pdf, last accessed August 2012.

1.1.3.2 Price competition in off-patent markets and first entrant advantage

Definition of generics Once the medicine is off-patent, the exact product can be copied by other firms via a generic version of the originator medicinal product. A generic is defined in comparison to a reference medicinal product which has lost its patent exclusivity. Directive 2001/83/EC of the European Parliament and the Council of 6 November 2001 on the Community Code relating to medicinal products for human use defines a generic medicinal product as

> "a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy". (Directive 2001/83/EC, Art.10, para 2(b))

It is not required for generic medicinal products to repeat pre-clinical and clinical trials. To ensure their efficacy and safety, the data provided in the originator product application is used, once the data exclusivity period is over[17]. Hence, generics benefit from an abbreviated procedure of marketing authorisation, making approval faster and less costly in order to decrease the barriers to entry for generics. As generic products only differ in their presentation, price becomes an important marketing instrument leading to "margin competition" with originator products.

Consequently, competition between generics and originator medicinal products corresponds to a perfect repeated Bertrand competition. Generic firms compete mainly on price with off-patent originators, and between themselves due to bioequivalence (Hollis, 2002). In Hollis' model, a one-shot game is assumed which is coherent with the price-setting process of pharmaceuticals. Firms choose their prices independently and simultaneously, and do not have capacity constraints. This assumption is deemed as plausible for medicinal products (Frank and Salkever, 1992). They are also assumed to have relatively low asymmetries in their marginal costs which is relevant as in the generic industry, no drastic innovation occurs which could lead to a reduction of the costs.

First entrant advantage and switching costs After patent expiration, entry of generic medicinal products operates in waves. In countries where the price of generic medicinal products is not regulated,

[17] Supplementary protection certificates (SPC) allow since 1993 the extension of patent protection depending on the period elapsed between the date at which the patent application was filed and the date of the first market approval of the drug, for a maximum of five years. The aim of the SPC was to ensure a minimum patent-protected period for a pharmaceutical product to make up for the time spent in approval procedures. Cf. http://europa.eu/legislation_summaries/other/l21156_en.htm, last accessed July 2013.

strategic pricing by the first entrant is important and can become a competitive advantage (Hollis, 2002). Hollis finds that the first entrant in the Canadian market for generics has, on average, a lasting competitive advantage of around 30% over four years. The existence of a first entrant advantage can be explained by important switching costs, which are difficult to overcome as both the pharmacists and the prescribing physicians prefer not to switch to a generic version.

Medicines can be defined as an "experience" good where physicians, while prescribing a medicine, face learning and uncertainty costs. From the side of the pharmacists, switching between generic versions may lead to high inventory costs, as well as increased transaction and contractual costs. It may be time consuming for them to explain to patients the bioequivalence of generic products. These costs are strengthened by the lack of incentives given to them to switch to a less expensive generic product.

Perceived quality and generic medicines Switching costs are also associated with the "perceived quality" of generic medicines by patients. Products can be differentiated in a vertical and horizontal way (Lancaster, 1979, Phlips and Thisse, 1982) as they are made of a bundle of characteristics with features that can be ordered in an objective way by consumers (vertical differentiation) and some that cannot (horizontal differentiation). While originators and generics products are therapeutically equivalent and hence of the same quality, their respective perceived quality for consumers is different.

"Licensed generics" as an implication of the first entrant´s advantages Direct implications of the first entrant's advantages in the generic industry concern the incentives given to brand-name companies to issue generic copies of their own originator products - called "licensed generics" or "authorised generics" - before their true generic competitors, thus raising barriers to entry.

Licensed generics are copies of an originator by the manufacturer of the originator product or an affiliated company right prior to patent expiry of the originator. Thus, licensed generic products are available on the market before true generic competitors and have a substantial competitive advantage as they can enter the market prior to patent expiry and discourage potential future generic competitors (Reiffen and Ward, 2007, p. 252).

Licensed generics and market segmentation The rationale behind marketing licensed generics is due to the presence of different consumer segments with different price elasticities. Even if the patient does not bear the full cost of the medicines, they have to pay either a fixed or a progressive copayment. In a reference price system, they also have to pay the full difference between the price of the product and the reference price, which increases patients´ price-sensitivity.

Frank and Salkever (1992) explain the segmentation of the prescription drugs market between, on the

one hand, consumers who are price-sensitive, and on the other hand, those who are less price-sensitive and instead have strong brand loyalty.

Kong (2009) chooses to segment pharmaceutical markets corresponding to the quality of the patient's insurance coverage. He shows that it is the quality of insurance coverage that determines their price elasticity and, therefore, their choices between the off-patent originator and the generic version. However, the patient's price elasticity characteristics are not observable. Thus, the pharmaceutical firm has to encourage the patient to reveal their price elasticity by offering different combinations of products characteristics and prices. The different dimensions of a pharmaceutical product are weighted variously by consumers with high price elasticity and those with low price-elasticity. Consumers with low price elasticity will continue buying the off-patent originator, which is priced higher, as they can afford to be brand loyal. Consequently, brand loyalty can also be reinforced through targeted advertising which leads the demand curve to become less price elastic (Schmalensee, 1982).

The pharmaceutical firm will offer a generic copy of its product, targeting consumers with a low price elasticity. The licensed generic copy should, however, be manufactured by a sister company, in order to not discourage high-price consumers who would otherwise be able to make an arbitrage. This price discrimination which enables the patient to choose the pharmaceutical which corresponds to their own price elasticity, is a second-degree price discrimination, also called "menu pricing" (Belleflamme and Peitz, 2010, p.217).

Menu pricing is offered by a monopolist to gain consumers with high price elasticity who would not otherwise buy its product because of the higher price. However, in the case of pharmaceuticals, menu pricing is offered by the originator firm in order to gain a first-mover advantage, right before the patent expiry and before the marketing of generic versions. This therefore leads consumers to sort themselves according to their price elasticity and increase barriers to entry before authentic generics come into the market.

Competition between generics as a Stackelberg game? Due to the presence of a lasting first-mover advantage, competition patterns between manufacturers of generics and off-patent originators can best be described as a Stackelberg game, which is enhanced by the presence of price-differentiation and national regulation practices on price and reimbursement.

The Stackelberg equilibrium describes situations where a firm has a competitive advantage over a group of other firms, which is the case of the originator firm (Scherer and Ross, 1990, p.222). Scherer and Ross assume that the brand name producer acts as a dominant firm which incorporates the price setting of generic firms in its pricing decisions. In turn, generic manufacturers take the originator firm's pricing

decisions as given.

1.2 Current challenges in pharmaceutical markets

Worldwide challenges in pharmaceutical markets, and particularly in the EU, consist of rising healthcare costs, while ensuring high quality services. On 15 January 2008, the EC launched a Sector Inquiry on pharmaceutical markets in order to determine, firstly the reasons for the delays of generic entry, and secondly the reason why fewer new pharmaceutical products are brought to the market. By investigating the issues around patent rights, competition between originator and generic companies, and among originator companies, the EC concluded on the necessity to intensify competition law scrutiny, to establish a Community patent, and create a unified litigation system. It also emphasised the need to speed up the marketing authorisation process and improve pricing and reimbursement systems in order to develop a competitive environment for generic medicines (DG COMP, 2009).

Focus will be set on the information advantage of originators over generic versions due to prescription habits and brand loyalty (1.2.1) as well as on the trend towards the systematic implementation of cost-effectiveness assessment for new medicinal products (1.2.2).

1.2.1 Advantages of off-patent originators and barriers to entry for generic versions in off-patent markets

Once the presence of an information advantage in off-patent markets favouring originator products has been defined and explained, (1.2.1.1), a review of the empirical literature on this issue will be performed (1.2.1.2).

1.2.1.1 Existence of information advantage for the originator

Prescription habits and brand loyalty While generic versions can be considered as perfect copy of the originator, as their bioequivalence is proven, thus price competition between the originator and the generic version might take place. However, Combe and Haug (2006a) explain the presence of a certain demand inertia by prescribing physicians towards originator products. During the time the product was the only alternative available, physicians have gotten used to prescribing a product which creates prescription habits, and brand loyalty. As explained in the previous section, switching to the prescription of generics would require a learning effort from the physicians, when they can count on their own experience with the originator product. Combe and Haug stress the fact that medicines are an "experience good"; physicians are familiar with the functioning of an originator product, but they do not know whether a generic might have side effects, or even which are the generic versions available on the market. This brand loyalty effect is increased by the advertising expense of the originator during its patent protection.

Advertising expenses Advertising expenses are important in the pharmaceutical industry, especially at the launch of a new product. New drugs are, in most cases, accompanied by significant advertising expenses, regardless of the type of innovation. These advertising campaigns aim to build product recognition with prescribing physicians. When generic versions enter the market, the off-patent originator can then focus on segments which become, de facto, less elastic due to marketing expenditure. This strategy avoids for the originator to directly compete on price with generic products by decreasing their prices[18]. Kina et al. (2009) studied the business models of generic and originator firms and found significant differences. While heavy investments in R&D and in marketing belong to the business model of originator firms, generic firms require strong competences in manufacturing, channel management and patent litigation.

More than 21% of the global share of cost factors of an originator company (in percentage of the annual turnover) are dedicated to marketing and promotion efforts, while it is only 18% for the R&D costs (DG COMP, 2009). Table 1.2 provides an overview of the advertising expenditure for the originator and generic versions. Consequently, advertising expenditure represents the main component of an originator company's costs.

Table 1.2: Global share of costs factors as a percentage of annual turnover (2007)

	Originator firms	Generic firms
Manufacturing costs	21%	51%
Marketing and promotion costs	**21%**	**13%**
R&D costs	18%	7%
Administrative costs	7%	3%
Other costs	3%	4%

Sources: DG COMP, 2009

Information on medicines plays an important role in physician's prescribing behaviour. Therefore, through important marketing efforts, directed at physicians when launching their product and during the whole life cycle of their product, firms can alter physician preferences, create brand loyalty, and hence bridge an information gap. One large component of marketing effort is detailing to physicians (symposia, visits by pharmaceutical representatives, free trial products...). These advertising expenses by originator firms aim to reinforce brand loyalty in prescribing physicians. Physicians develop predispositions which remain over time due to brand loyalty and hence impede price competition from taking place after the marketing of generic versions of the originator product. Originator firms can keep charging higher prices, by targeting the remaining loyal market segment (Dalen et al., 2006). Without providing any financial incentive, physicians act as their patient's agent. They take into account the price of the product only with regard to out-of-pocket payments, but not the global costs which are borne by the health insurance. These

[18]Cf. Handbook on pricing research in marketing, chapter 23, Pharmaceutical Pricing, 2009.

particular characteristics of pharmaceutical markets, where the choice, the in-taking, and the purchase of the medicinal product are made by different entities, should be taken into account, in particular when shaping measures, aimed at promoting price competition and the uptake of generics. For this reason, the implementation of a reference pricing scheme, which increases what the patient has to pay-out-of-pocket, can have an impact on physician´s prescription choices and hence might increase the use of generics.

1.2.1.2 Empirical studies on the information advantage of originator products

Advertising in the pharmaceutical industry Berndt et al. (1985, p.101) investigated the presence of a high marketing sales ratio in the pharmaceutical industry. They found that the largest component, around 70%-80%, corresponds to informing physicians, such as visiting doctors and providing them with information on the product. Advertising in medical journals was also found to be important. With regard to the information content of marketing, Berndt et al. found that marketing primarily puts emphasis on product differentiation and on non-price aspects.

Advertising by originators also takes place before patent expiration. Morton (2000) investigated the role of pre-expiration brand advertising on the market entry of generics in the US. Pharmaceutical advertising has a "market-expansion role" (Morton, p.1097) at the beginning of product's life cycle, when the drug is new to the physician. At the end of a life cycle, the purpose of advertising is to defend the market shares of the originator product, and to create switching costs for the physician.

The impact of advertising expenses on the demand for medicinal products was extensively investigated in the theoretical and empirical literature, which insists on the existence of an imperfect price competition between originator products and their generic versions due to the presence of a perceived quality differentiation. While advertising disseminates information, which helps in making rational choices, it can also create artificial product differentiation and can lead to the creation of barriers to entry.

Hurwitz and Caves (1988), by investigating a sample of medicines, which were no longer patented, and were facing generic competition, showed that advertising had persuasive effects. Advertising expenses preserve the incumbent market shares, as it produces perceived quality differentiation between the incumbent product and the generic versions. Rizzo (1999), by taking all originator anti-hypertensive medicines in the US for the period 1988-1993, investigated the impact of advertising on the demand price elasticity. Rizzo found that advertising, especially detailing efforts, decreased the demand price elasticity by creating brand loyalty. Thus, consumers are more willing to pay higher prices.

Both empirical studies concluded on the existence of persuasive as well as informative effects of pharmaceutical advertising on physicians. Informative advertising also, by decreasing the uncertainty of a product, creates brand loyalty and decreases price elasticity. They show that current and past advertis-

ing expenditures preserve the originator's market shares by increasing brand loyalty and the perceived differentiation between the originator and generic versions.

Prescription behaviour and information advantage Hellerstein (1998) studied physician behaviour in their prescription choice: either the originator, or a generic version. By analysing a data set of physicians' prescription decisions, she found that some physicians were more likely to prescribe generic versions, while others were more likely to keep prescribing the originator product. Interestingly, she also noted that the personal characteristics of the patient represented a negligible variable in the prescription decision. The decision taken by the physician could mainly be explained by their prescription behaviour and other issues related to information imperfection (especially advertising) and agency problems which are embodied in the prescription decision.

Königbauer (2007) showed in a theoretical model that persuasive advertising in the period before patent expiration creates prior product differentiation, in comparison to future generic versions in the market. She concluded from her model, that advertising expenses have an important impact on physicians's prescription choices.

Cabrales (2003), who studied competition issues in generic markets in a vertical product differentiation model, also stressed that the difference in quality in these markets is to be considered in terms of "perceived quality" as generics are per definition bioequivalent to the originator and safety, efficacy, and quality checks are performed by health authorities.

1.2.2 New cost-effectiveness paradigm in on-patent markets

Once the use of health economic evaluations has been defined and explained (1.2.2.1), a review of the different national bodies and of their methodology is performed (1.2.2.2).

1.2.2.1 Reimbursement decisions and use of pharmacoeconomics studies

Trends towards Health Technology Assessments ("HTA") Due to the increased pressure on healthcare budgets, reimbursement decisions taken by healthcare authorities are increasingly driven by considerations of cost-effectiveness. As a consequence the regulatory approval given at a national or centralised level is of little use for pharmaceutical firms when the drug is not reimbursed, especially for costly innovative drugs. The sole criteria of efficiency, quality, and safety which have to be demonstrated during the marketing authorisation process are not sufficient due to the product's life cycle and the experience gained with the product together with the data gathered. In addition to satisfying the requirements for

quality, safety, and efficacy which are assessed by the healthcare regulator, medicinal products are required to obtain a positive reimbursement decision from third-party payers, in order to gain market access.

The reimbursement decision is a function of the product's cost effectiveness. Consequently, pharmacoeconomic instruments and methods have been developed in order to define when a product can be considered as cost-effective, and represents "good value for money". The Health Technology Assessment (so-called "HTA") process itself, is an interdisciplinary process created to assess, in a systematic and transparent way, each drug or technology process with attention given to medical, economic, law, social and ethical aspects (Greiner, 2007, p.449). HTA reports typically deal with the assessment of new innovative medicinal products, and aim to decide whether they should be reimbursed or not, and if so, at what price.

Assessment of the relative effectiveness for reimbursement purposes In this assessment performed by payers, the issue of relative effectiveness plays a key role as third-party payers base their reimbursement decisions predominantly on the health benefits of the drug relative to existing treatment options (Eichler et al., 2010). As previously mentioned, payers have a different perspective from that of healthcare authorities. In their HTA, payers put emphasis on identifying the most valuable medicines, both in terms of clinical efficiency and cost-effectiveness.

This increasing importance of assessing the relative effectiveness is the result of escalating healthcare costs, and the need to balance budgets. This situation led payers to become more restrictive in their reimbursement decisions of new expensive medicinal products. This is the reason why reimbursement coverage has become a major issue for new drugs. Firstly, the decision-making power of payers, often health insurers, has increased at the expense of prescribing physicians, who are restricted by payers' reimbursement decisions. Secondly, the success in terms of sales volume of a new innovative drug is now less driven by the usual marketing efforts, but rather by its ability to demonstrate an added therapeutic value to third-party payers, compared to existing treatment alternatives. Lastly, reimbursement decisions are often taken by expert committees based on a sophisticated methodology which might be intransparent for pharmaceutical companies, and might not come to the same result as healthcare regulatory authorities. Thus, volatile situations might arise. An approved medicinal product in terms of quality, safety, and efficacy might not be reimbursed by third-party payers, with the consequence that it will not be available to most patients who cannot afford it.

Regulatory approval vs. reimbursement HTA adopt different considerations than those of regulatory authorities in the marketing authorisation process, as the basis of payer's reimbursement decision differs from the regulatory decision. Regulatory authorities focus on the benefit-risk assessment of the new

drug, meaning whether the drug will do more good than harm in a defined group of patients. As a general rule, each new drug is evaluated on its own benefit, but does not require a new drug to be assessed against other existing available treatments. This process of marketing authorisation is often referred to, as the first three hurdles (i.e. quality, safety, and efficacy representing the benefit–risk assessment). It is only after this assessment that marketing authorisation holders will then seek reimbursement from third-party payers at a national level.

By contrast to health regulatory authorities, the purpose of third-party payers in their HTA is to optimise the health outcomes for patients by considering all available treatment options, and at the same time, to account also for budgetary constraints. To this purpose, they perform a full economic comparison of healthcare strategies. Consequently, they compare health outcomes and cost consequences of two or more treatments. This assessment leads to a quantification of the difference in health benefits accrued by treatment alternatives.

1.2.2.2 Examples of HTA bodies and methodologies in selected member states

HTA decisions are taken by special HTA bodies at a national level only. It means that, for the same medicinal product having, for example, a unique centralised marketing authorisation at the European level, different HTA reports coming from different healthcare authorities might coexist and, possibly, come to different conclusions concerning the effectiveness of the medicinal product. These divergent assessments result from the different HTA bodies that exist in member states and the weighting of the various factors which are taken into account in the assessment.

Germany: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen In Germany, the responsible body is the Institute for Quality and Efficiency in Healthcare ("Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen", hereinafter "IQWiG") which was founded in 2004 with the implementation of the law on the modernisation of the Social Security ("GKV-Modernisierungsgesetz", hereinafter GMG[19]) to improve the quality of the healthcare products and services delivered[20]. In order to support the Federal Joint Committee ("Gemeinsamer Bundesausschuss", hereinafter "G-BA") and the National Association of Statutory Health Insurance Funds ("Spitzenverband der Gesetzlichen Krankenversicherung", hereinafter "GKV-Spitzenverband"), its tasks are described in paragraph 139a-c of the Social Code V ("Sozialgesetzbuch V", hereinafter "SGB V"[21]), and consist among others, of assessing the state of the current medical knowledge for selected diseases, drafting of reports concerning

[19] Available at http://www.rechtliches.de/info_GKV-Modernisierungsgesetz.html, last accessed January 2012.
[20] Cf. website of the IQWiG, www.iqwig.de, last accessed June 2013.
[21] Available at http://www.sozialgesetzbuch.de/gesetze/05/index.php?norm_ID=0513900, last accessed August 2012.

the safety and quality of healthcare products and services in the social security, benefit assessment of medicinal products. The implementation of the law strengthening competition in social insurance ("GKV-Wettbewerbsstärkungsgesetz", hereinafter "GKV-WSG") added article 35b[22] in the SGB V which provides for the methodology of benefit assessment of innovative medicinal products by the IQWiG. According to paragraph 35a[23] of the SGB V, the IQWiG can be mandated by the Federal Joint Committee to provide for an early benefit assessment of an innovative medicinal product.

AMNOG, the law which reorganised the pharmaceutical market and entered into force on 1 January 2011 goes further, as it provides that pharmaceutical companies shall prove the medical added value of each new innovative medicinal product. Furthermore within one year, they shall negotiate a price with the mandatory health insurance. Medicinal products with a new active ingredient have to undergo within three months a benefit assessment which leads within nine months to a price-setting.

The aim of these systematic benefit evaluations is to assess the additional costs brought by new innovative products, compared to the additional therapeutic benefit of existing alternatives and to set the reimbursed price of medications dependent upon the added medical value, after a subsequent health economic evaluation. General principles of the IQWiG take into account the local conditions with regards to epidemiology, healthcare resource, clinical practice, reimbursement of providers, and organisational structures so that project-specific methods and criteria are applied[24]. The Federal Joint Committee G-BA[25] makes the final assessment.

The outcome of the cost-benefit assessment is crucial as the results of the assessment are the basis for the negotiations on the reimbursement price[26]. The dossier for the cost-effectiveness assessment to be submitted by the marketing authorisation holder shall contain the approved indications of the medicinal product, the medical benefits, the additional medical benefits in relation to the appropriate comparison treatment, the number of patients and patient groups for which there is a significant additional therapeutic benefit, the costs of therapy for the statutory health insurance, and lastly the requirement for a quality-assured application[27]. The added value is measured with a scale which goes from one (important improvement) to six (lower value, meaning that the benefit of the product is indeed lower than the existing comparable therapies). Two cases can occur dependent upon whether an extra benefit for the innovative product was found, or not. If an extra benefit of the innovative product is proven, the pharmaceutical

[22] Available at http://www.sozialgesetzbuch.de/gesetze/05/index.php?norm_ID=0503502, last accessed August 2012.
[23] Available at http://www.sozialgesetzbuch.de/gesetze/05/index.php?norm_ID=0503501, last accessed October 2012.
[24] For more information, cf. IQWiG, "General Methods for the Assessment of the Relation of Benefits to Costs", available at https://www.iqwig.de/download/General_Methods_for_the_Assessment_of_the_Relation_of_Benefits_to_Costs.pdf, last accessed August 2012.
[25] Cf. website of the G-BA, http://www.g-ba.de, last accessed February 2012.
[26] Cf. art. 130b of the Social Law Code (SGB V), available at http://www.sozialgesetzbuch-sgb.de/sgbv/130b.html, last accessed August 2012.
[27] Cf. par. 35a (1) of the Social Law Code (SGB V) available at http://www.sozialgesetzbuch-sgb.de/sgbv/35a.html, last accessed October 2012.

company enters into negotiation with the GKV-Spitzenverband [28] to negotiate a price for reimbursement based on the results of the assessment. If an added medical benefit is found, the price will be higher than the price of the comparable therapy. If no extra benefit is found, the innovative product falls in the reference pricing scheme, together with comparable substances and undergoes the reference price[29]. The reimbursement price level will be set based on the price of the comparable drug.

France: Haute Autorité de Santé In France, it is the Transparency Commission ("Commission de la Transparence")[30] by the High Authority for Health ("Haute Autorité de Santé", hereinafter "HAS")[31] which is in charge of assessing the medical benefit of pharmaceuticals ("Service Médical Rendu", so-called SMR) and the innovation level by assessing the improvement of the medical benefit ("Amélioration du Service Médical Rendu", so-called ASMR) compared to alternative products. The law provides that pharmaceuticals without any ASMR rating or implying no savings on medical treatment costs, are not reimbursed by health insurance funds, and that their price can be set freely[32]. For pharmaceuticals with an ASMR, the price fixing decision of the pricing commitee ("Comité Economique des Produits de Santé", hereinafter CEPS) is based on the ASMR rating granted by the Transparency Commission, the expected sales of the pharmaceutical, and the prices of pharmaceuticals in other EU member states (external reference pricing) as well as the price of possible alternative therapies in France[33].

The SMR and ASMR ratings given by the Transparency Commission are key criteria in setting the price and determining the reimbursement rate of pharmaceuticals as they assess the medical benefit and the innovation rate of the pharmaceutical. The level of these ratings is the basis for the reimbursement status and the price of the pharmaceutical. Unlike the SMR rating, the ASMR rating compares the therapeutic value of a pharmaceutical to the existing alternatives in the same therapeutic class, and assesses the improvement brought. Five main classes of ASMR ratings exist, ranging from ASMR I for medicinal products bringing a major therapeutic value, to ASMR V for medicinal products without any therapeutic value, but still being recommended for reimbursement with a price criterion that does not lead to any additional non-justified expenses. The SMR, which is used to determine the reimbursement level for a pharmaceutical, takes into account the efficacy of the pharmaceutical under assessment and its side effects, the characteristics of the disease it is indicated for, the existence of alternative therapies,

[28] For more information, cf. par. 130b, Social Law Code V.

[29] Cf. chapter 3.

[30] Cf. http://www.has-sante.fr/portail/jcms/c_412113/commission-de-la-transparence, as defined by Art. R163-15 to Art. R163-21 of the Social Security Code.

[31] Cf. http://www.has-sante.fr/portail/jcms/j_5/accueil. created by law n° 2004-810 of 13 August 2004, Title 2, Section 1, Art. 35, 36 et 37, http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000000625158.

[32] Cf. art. R163-5 of the Social Security Code, http://www.legifrance.gouv.fr/affichCodeArticle.do?cidTexte=LEGITEXT000006073189&idArticle=LEGIARTI000006746711&dateTexte=20100909, last accessed August 2012.

[33] Regarding external reference pricing, no formal procedure exists, cf. annual reports of the CEPS, available at http://www.sante.gouv.fr/les-activites-du-ceps.html, last accessed August 2013.

the role of the pharmaceutical within the overall therapeutic strategy, as well as the impact on public health[34]. Different levels of SMR rating have been defined, ranging from major or important to insufficient therapeutic value, through moderate or low therapeutic value, while still allowing for reimbursement[35].

UK: National Institute for Health and Clinical Excellence (NICE) In the UK, it is the healthcare authority NICE, created in 1999 and funded by the Department of Health (so-called DoH), which is the HTA body in place and is therefore responsible for deciding which medicinal products and treatments are reimbursed in England, together with the All Wales Medicines Strategy Group in Wales[36].

NICE´s tasks consists of assessing new medicines and issuing evidence-based guidance to solve uncertainty about treatments, thus offering the best value for money for the NHS and providing guidelines on the way a particular condition should be treated[37]. HTA are one guidance area among others - such as guidance dealing with clinical practice or public health - and are primarily based on efficacy and cost-effectiveness. Concerning the HTA, NICE´s recommendations are based on the review of clinical and economic evidence, meaning whether it represents value for money. Decisions are thus based on the review of evidence, cost effectiveness (including the Quality-Adjusted Life Year, hereinafter QALY)[38]) and the contributions from patient organisations, health professionals and experts. The recommendations are classified into four categories: recommended, optimised, only in research, and not recommended[39].

NICE´s recommendations have an important impact on the use of a drug, as it may recommend the product in question, after its assessment of its value for a smaller sub-population of patients than what was initially foreseen in the marketing authorisation. Since January 2005, the NHS in England and Wales is legally obliged to provide funding for medicines and treatments recommended by NICE.

Italy: Agenzia Italiana del Farmaco (AIFA) In Italy, while a healthcare service at national level exists ("Servizio Sanitario Nazionale", hereinafter SSN)[40], healthcare provision is organised at the level of regional authorities ("Aziende Sanitarie Locali", hereinafter ASL). An important player in the healthcare

[34]Cf. art. R163-3 of the Social Security Code, modified by Decree n°2004-1398 of 23 December 2004.

[35]For more details, cf. Natz,A., Campion,M.G. (2012a)

[36]Cf. http://www.nice.org.uk, last accessed June 2013.

[37]The Health and Social Care Act 2011 plans for NICE to become a Non Departmental Public Body starting from 1 April 2013 and expand in order to produce quality standards for the social care sector.

[38]The QALY is used to measure the health benefits delivered by a given product. It is an instrument which assesses how a treatment affects the quantity of life (meaning the number of years gained with the treatment) and the quality of life of a patient (corresponding the impact of the treatment on the well-being of the patient, is regained ability to work or not. The present value of expected QALY flows with and without treatment, or relative to another treatment, is compared in order to derive the net relative health benefit from the product in question. When information on the relative costs of the treatment is added, the Incremental Cost-Effectiveness Ratio (so-called ICER) can be derived. Suggested expenditure can be therefore compared against current resource used at the margin which leads to the calculation of the cost-effectiveness threshold. As a guideline rule, NICE considers as cost effective medicinal products with an incremental cost-effectiveness ratio of less than £20,000 per QALY.

[39]The guide to the HTA procedures of NICE can be found at http://www.nice.org.uk/aboutnice/howwework/devnicetech/guidetothemethodsoftechnologyappraisal.jsp, last accessed August 2012.

[40]Cf. website of the Italian Health Ministry, http://www.salute.gov.it/, last accessed June 2013.

provision is the Agenzia Italiana del Farmaco (hereinafter AIFA) which is in charge of diverse key aspects of the regulation of pharmaceuticals, especially pricing and reimbursement aspects. AIFA incorporates different commissions, in particular the Scientific-Technical Commission ("Commissione Tecnico Scientifica", hereinafter "CTS") which evaluates medicinal products with regard to quality, safety, and efficacy for marketing authorisation and according to their reimbursement status. Another important commission is the Pricing and Reimbursement Committee ("Comitato Prezzi e Rimborso", hereinafter CPR), which is in charge of the negotiation on the prices of reimbursed medicinal products (so-called "class-A medicinal products") with pharmaceutical companies (OEBIG, 2008).

Levels of reimbursement for pharmaceuticals are set through negotiation between the CPR and pharmaceutical companies, in accordance with law n. 326 of 24 November 2003[41]. Among the criteria used are, cost-effectiveness of the medicinal products where no effective alternative therapy exists, the risk-benefit ratio compared to alternative pharmaceuticals for this specific indication, the therapy costs per day in comparison to similar products, the economic impact on the national healthcare budget, and the targeted population in other member states[42].

Role of the EU initiative: EUnetHTA Differences among HTA bodies exist as previously described. For this reason, as HTA were considered by the EC and the Council of Ministers as a political priority, an initiative was launched in 2004 at EU level to create an effective and sustainable network of HTA bodies in the EU, in order to promote "reliable, timely, and transparent" information on medicinal products across the EU member states, and support member states possessing limited experience with HTAs[43]. The objective of the EUnetHTA network is:

- "facilitating efficient use of resources available for HTA,
- creating a sustainable system of HTA knowledge sharing,
- promoting good practice in HTA methodes and processes".[44]

In particular, the aim of the EUnetHTA Joint Action 1 (2010-2012) was to bring together HTA bodies and other producers of HTA to draw conclusions on the relative effectiveness of medicinal products by providing principles and methodological guidance and promoting structured exchange and storage of information. The most innovative provision, brought by the EUnetHTA network, is the so-called "HTA Core Model"

[41] Cf. http://gazzette.comune.jesi.an.it/, last accessed June 2013.

[42] The list of the relevant criteria can be found in the Deliberazione CIPE 1/2/01: "Individuazione dei criteri per la contrattazione del prezzo dei farmaci", available at http://www.informatori.it/informatori/filepdf/Prezzo-farmaci.pdf, last accessed June 2013.

[43] Cf. http.//www.eunethta.eu. The EUnetHTA network was set up by the creation of the EUnetHTA collaboration 2009, the EUnetHTA Joint Action 2010-2012 and the EUnetHTA Joint Action 2 2012-2015, last accessed July 2013.

[44] Cf.http://www.eunethta.eu/about-us, last accessed July 2013.

which enables the production and the exchange of effective HTA decisions among member states in a common structure format in nine areas: health problems and current use, description and technical characteristics, safety, effectiveness, costs and economic evaluation, ethical, organisational, social, and legal aspects (Kristensen, 2012). The core model has been developed as a platform for HTA bodies to promote collaboration and exchange among member states.

1.3 Questioning the economic functioning of pharmaceutical markets

Based on the analysis of regulation patterns in pharmaceutical markets and the related challenges stressed, the purpose of the following section is to raise three research questions related to substitutability patterns (1.3.1), articulations between cost-containment measures and incentives to innovate (1.3.2), and finally the role of risk-sharing schemes to solve existing information asymmetries (1.3.3).

1.3.1 How to define substitutability among medicinal products?

Substitution patterns are not straightforward in pharmaceutical markets. To that purpose, the analysis of the Anatomical-Therapeutical-Chemical (hereinafter ATC) classification which groups medicinal products according to various criteria is of interest (1.3.1.1). Substitutability patterns in these markets are analysed, in particular in the framework of the relevant market definition which will be further investigated (1.3.1.2).

1.3.1.1 Substitution and Anatomical-Therapeutical-Chemical (ATC) classification

As mentioned in previous sections, competition in pharmaceutical markets is heavily regulated on the demand side and the supply side due to the characteristics of these markets. While a rationale use of medicinal products is encouraged, through price competition in off-patent markets and therapeutic competition based on cost-effectiveness considerations compared to an existing alternative, the issue of substitution patterns is a key determinant in the success of regulation. When implementing generic substitution or implementing a measure to increase the elasticity of demand, the underlying reasoning is that products can be substituted.

However, when assessing demand substitution patterns, an important question concerns the identity of the "customer" of the medicinal product: is it the patient who consumes, the prescribing physician who prescribes, or the health insurer who is the final payer? On what basis can two products be considered as substitutable? The answer to these questions is key to the success of any healthcare regulation.

Description of the ATC classification A specific classification for medicines, the so-called "ATC" classification system[45] which was developed by the European Pharmaceutical Marketing Research Association (hereinafter EphMRA[46]) is a method of grouping medicinal products. It contains sixteen different levels with sublevels. In the different levels, products are classified by anatomical site of action, indication,

[45] See EPHMRA Anatomical Classification Guidelines 2010, available at http://www.ephmra.org/PDF/ATC%20Guidelines%202010.pdf, last accessed November 2011.
[46] Cf. http://www.ephmra.org/.

Table 1.3: Example of levels in the ATC classification

1st level, anatomical main group	N: Nervous system
2nd level, therapeutic main group	N02: Analgesics (N01: Anesthetics)
3rd level, pharmacological/therapeutic subgroup	N02B: Other analgesics and antipyretics (N02A: Opioids – Morphine, Opium)
4th level, chemical/pharmalogical/therapeutic group	N02BA: Salicylic acid and derivatives (N02BE: Anilides – Paracetamol)
5th level, molecule/product subgroup	N02BA01: Acetylsalicylic acid

Sources: ATC Classification, 2011

mechanism of action, or composition. The first level concerns the anatomical main group, the second level the therapeutic main group, the third level the therapeutic subgroup, the fourth level the chemical group, and finally the fifth level the molecule/product subgroup.

In order to explain the ATC method of classification, a well-known medicine, such as "Aspirin" can be used as an example. Table 1.3 gives the classification of Acetylsalicylic acid which is the main active ingredient of Aspirin. It belongs to the group of analgesics used to relieve minor pain, as well as to the antipyretics group used to reduce fever, to the anti-inflammatories group used to reduce inflammation, and to the platelet aggregation inhibitors group used to decrease platelet aggregation and inhibit the formation of thrombus[47]. As a pain reliever, which is the classification this thesis has chosen to investigate, it differentiates from opioids at the third level and from the paracetamol at the fourth level.

EphMRA´s ATC classification must be distinguished from the ATC classification designed by the World Health Organization (hereinafter "WHO"), as they diverge mainly by the methods in which products are classified[48]. While the WHO classifies substances mostly according to their therapeutic or pharmaceutical characteristics and in one class only, the EphMRA classifies products according to their indications and use. This explains why in the EphMRA the same compound can be found in different classes[49].

1.3.1.2 Relevant product market and substitution patterns

Defining the relevant product market The approach behind the relevant products market in the pharmaceutical sector is of particular interest in defining which level in the ATC classification is to be considered as relevant in order to consider two products as substitutable.

[47] Cf. Summary of Characteristics (hereinafter, "SPC") of the Bayer Aspirin for example.

[48] Products can be "defined as a pack or unit this can be dispensed, prescribed, etc. The products are classified according to their main therapeutic indication. Each product is assigned to one category". Cf. EPHMRA/PBIRG Classification Committee, "What we are, what we do- 2010", http://www.ephmra.org/pdf/2010%20Who%20we%20are%20brochure_FINAL.pdf, p. 5, last accessed November 2011.

[49] Cf. EPHMRA/PBIRG Classification Committee, "What we are, what we do- 2010" http://www.ephmra.org/pdf/2010%20Who%20we%20are%20brochure_FINAL.pdf, last accessed November 2011.

The concept of the relevant product market is however not straightforward to apply to pharmaceutical markets. The definition of the relevant market is a key step for competitive analysis in mergers and abuse of dominant position as it defines the field of competition and enables the identification of market participants. In order to clarify the concept of the relevant market, the EC issued a "Commission Notice on the definition of relevant market for the purposes of Community competition law"[50] (97/372/03), stating that:

> "Market definition is a tool to identify and define the boundaries of competition between firms. It serves to establish the framework within which competition policy is applied by the Commission. The main purpose of market definition is to identify in a systematic way the competitive constraints that the undertakings involved face. The objective of defining a market in both its product and geographic dimension is to identify these actual competitors of the undertakings involved that are capable of constraining these undertakings' behaviour and of preventing them from behaving independently of effective competitive pressure." (Cf. Commission Notice, Par. 2)

Accordingly, the concept of a relevant market plays a key role in merger control where the creation or reinforcement of a dominant position in a given market which would impede competition in a substantial part of the Community should be prevented, or in competition cases investigated whether a firm possesses a dominant position in a given market and might be abusing it. While the concept of the relevant market is "closely linked"[51] to the objectives of the European competition policy, the importance of market definition was reiterated in the US in the New Horizontal Merger Guidelines[52]. In these guidelines, the relevant market helps to define the line of commerce in the given market and its participants in order to calculate market shares and to identify the likely competitive effects of a merger. It states that the definition of the relevant market which is solely based on demand substitution patterns, is not needed for competition purposes, and that the range of substitutes available to consumers have to be investigated at some point of the competitive analysis.

Further area for research: Which criteria define the scope of the relevant market?

The analysis of the concept of the relevant product market and its application to pharmaceutical markets will provide the substitution patterns at stake in these markets. In particular, an econometric analysis of

[50] Available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31997Y1209(01):EN:NOT, last accessed October 2011.

[51] See the Commission Notice, Par.10.

[52] Horizontal Merger Guidelines, US Department of Justice and the Federal Trade Commission, 19 August 2010, http://www.ftc.gov/os/2010/08/100819hmg.pdf, last accessed November 2011 .

the EC's decisions in merger cases allows to empirically define the important criteria to be incorporated while defining the relevant market in pharmaceutical markets, and observe the trends concerning the scope of the relevant product market (Chapter 2).

1.3.2 How to promote price competition in off-patent products while providing incentives to innovate for pharmaceutical companies?

While price competition is expected to be sharpened at the entry of generic versions in the market, barriers to entry exist (1.3.2.1). Hence, several member states implemented a system of reference pricing to promote price competition in off-patent markets (1.3.2.2).

1.3.2.1 Factors impeding price competition

After patent expiry, the competitive marketplace for the product changes, as price competition is sharpened with the arrival of lower-priced generic versions. This increase of price competition can be observed through the price differential among originator medicinal products and generic versions. While prices vary from one to four across countries for pharmaceuticals covered by patents, these price differences are heightened for generics, as the difference between the cheapest version and the most expensive can be up to sixteen times following the loss of patent (EP report, 2011).

However, price competition does not function perfectly because of the low elasticity of demand within pharmaceutical markets. This low price elasticity, which is due to the presence of health insurers acting as final third-party payers, impedes the functioning of price competition. This is also reinforced by the presence of an originator information advantage. As mentioned previously, originators have been on the market for a longer time and have invested in advertising, in order to ensure brand loyalty and brand recognition after patent expiry. Hence, penetration of generics in the EU differs across member states. The estimated share of generics in pharmaceuticals sales value in 2008 ranged from 7.1% in Spain, to 66% in Poland. This is the reason why measures to promote the uptake of generics have been implemented to help counterbalance the impact of this information advantage. In order to promote the use of generics, different regulatory instruments exist. They range from mandatory generic prescription and substitution, to internal reference pricing schemes, through external reference pricing. Regulation policies and competition measures focusing on the demand-side (quantity control) and the supply-side (price control), are launched by governments and aim to increase the consumption of generics which are priced lower than originator products.

Internal reference pricing as an instrument to increase the elasticity of demand Internal reference pricing is one of these measures and is used in most of the EU member states to increase the prescription and delivery of generics. It is a reimbursement scheme, in which a reference price is set, and corresponds to the maximum reimbursement level for a cluster of pharmaceuticals based on certain chemical, pharmacological, or therapeutic criteria. Thus, an important condition is to constitute clusters containing therapeutically substitutable medicinal products.

As previously examined, different levels of substitution exist, which range from level three (therapeutic) to level five (molecule) of the ATC classification system. Reference pricing has been designed to promote cost-efficient prescription behaviour by physicians, to regulate prices and to increase the price elasticity of demand. Insurers or regulators set a maximum reimbursement price which is the reference price for a group of products which are identical from a molecular or therapeutic point-of-view. The pharmaceutical manufacturer is free to set the price, but the patient will only be reimbursed up to the reference price. If the patient refuses the substitution or the delivery of a generic version, which is cheaper without any justified medical reason, they have to pay the full price difference between the price of the originator product and the reference price. Beyond the reference price, they have to pay out-of-pocket. The price set is often based on the lowest generic price of the cluster or the average price[53].

Theoretically, reference pricing increases price sensitivity in pharmaceutical markets, because it induces patients to switch from expensive pharmaceutical treatments to low-priced alternatives. Consequently, reference pricing intensifies price competition and leads to a reduction in pharmaceutical expenditures.

1.3.2.2 Internal reference pricing and innovation incentives

At the same time, pricing and reimbursement decisions interact with industrial considerations in the pharmaceutical sector, in terms of employment and research and development so that it should be regulated carefully. Annually, more than €26 billion are spent in the pharmaceutical sector on R&D. Furthermore, this sector employs directly more than 630,000 people in the EU (EP report, 2011, p.11).

Therefore, while deciding on regulation policies, healthcare regulators must take into account the impact of their policies on pharmaceutical companies' incentives to innovate. When deciding on their investment level, pharmaceutical firms take into account the long-term market prospects for their new products. The implementation of a reference price, which is artificially set as a basis for the reimbursement, leads indeed to a decrease in price for non-innovative pharmaceuticals and might have negative consequences on pharmaceutical companies'decisions to innovate.

[53]The issues around the implementation of a reference pricing scheme will be analysed in depth in the third chapter.

Further area for research: Integrating the originator information advantage in the modeling of reference pricing and analysing the impact on innovation incentives Theoretical models in the economic literature focus on the impact of reference pricing schemes on prices, and the health of patients, but none includes the information advantage of originators, which was empirically proven in studies on advertising and the prescribing physician's brand loyalty.

For this reason, a model integrating the information imperfection, which is reflected in the prescribing physicians' choices is interesting, in order to demonstrate how a reference price, by increasing the elasticity of demand, can be an instrument to counterbalance the effects of information imperfection, and increase price-competition in off-patent markets.

Few studies investigate the impact of reference pricing on the innovation incentives of pharmaceutical firms. By completing the previous model and integrating the possibility of innovation, it is possible to show that reference pricing can be considered, in specific cases, as an instrument to promote high-value innovative products. Consequently, it should be seen by policy decision makers as complementary to other measures taken to promote innovation in pharmaceutical markets (Chapter 3).

1.3.3 How to provide innovative products to patients while preserving health-care budgets?

While innovative medicinal products are surrounded by uncertainty, especially with regard to their efficacy to treat patients (1.3.3.1), risk-sharing schemes, by making the price paid to the firm a function of the proven success rate, represent an alternative (1.3.3.2).

1.3.3.1 Innovative medicinal products and related uncertainty

Added therapeutic value: effectiveness versus efficacy A new medicinal product is said to have added therapeutic value if clinical data shows that it offers patients better efficacy, and/or better safety, and/or simpler administration, than existing alternatives. For the health economic assessment performed by health insurers, the time interval between marketing authorisation and application for reimbursement is often short, thus near-identical clinical data sets and information on the new drug are used. No data is available at this time on the effectiveness of the new drug, thus a degree of uncertainty around the effectiveness of the innovative medicinal product exists. The health insurer can only have an incomplete assessment of the efficacy of the medicinal product on which to base its reimbursement decision. In their report, the High Level Pharmaceutical Forum organised by the EC published the respective definitions and core principles of the relative efficacy and relative effectiveness. The relative efficacy "can be defined

as the extent to which an intervention does more good than harm, under ideal circumstances, compared to one or more alternative interventions", in contrast to the relative effectiveness which "can be defined as the extent to which an intervention does more good than harm compared to one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of health care practice"[54].

While the efficacy refers to the treatment's success rate in ideal conditions, the effectiveness of a product is assessed in real conditions. Therefore, a contrast between efficacy and effectiveness exists as typically the health benefits of drugs are greater under the ideal circumstances of clinical trial settings, than in real life. The effectiveness and efficacy of the same product might indeed be different for multiple reasons.

This difference refers to uncontrolled or placebo-comparator information versus active-comparator information. At the time of assessment by third-party payers, real-life information is usually not available, thus only the efficacy, or the relative efficacy of the new innovative drug can be assessed. For this reason, a gap also often exists between efficacy, and effectiveness due to the patients' compliance in real life, and the possible uncontrolled interactions with other drugs when patients have different pathologies (Capri, 2011, p.4). Moreover, the assay sensitivity may be lacking for several reasons, including inappropriate patient selection (for example, inadvertent enrollment of patients with viral instead of bacterial otitis when comparing two antibiotic agents), poor treatment adherence, or inappropriate adjudication of the outcome parameter. Thus, in practice, the effectiveness is lower than the efficacy.

Uncertainty around the efficacy Assessing the relative efficacy (under ideal circumstances) of a new drug is not straightforward as it also depends on the comparator used in the studies. For example, a new antibiotic medicinal product compared with existing antibiotics already achieving success rates greater than 90% would be less likely to be efficient. Furthermore, considering the possible misdiagnosis, potential poor patient adherence, and other variables, it is unrealistic to expect that even the best new antibiotic treatment could achieve significantly higher cure rates than the medicinal products already available. However, the demonstration of the new innovative product´s superiority might not be possible, especially when the new drug exerts its pharmacological effect through the same mode of action as the reference compound.

The issue of the comparator to choose is not straightforward. For any given indication, there may be more than one option. For example, a broad range of drugs is available for first-line treatment of hypertension, all of which are potential comparators. The question is whether the comparator should

[54]More information available at http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/rea_principles_en.pdf, last accessed June 2013.

be labelled for exactly the specific indication (legal criterion), or be pharmacologically the most closely related to the new compound (pharmacological criterion), or be deemed the best available alternative, based on high-quality evidence (evidence-criterion), or the most widely used treatment option in this indication within a given healthcare environment (utilisation criterion). These criteria are important as they are not necessarily consistent. Companies themselves tend, for economic reasons, to propose the most costly comparator which is more favourable for them.

Moreover, for certain areas such as in the case of orphan drugs, the demonstration of superiority might theoretically be possible but from the point of view of the size and complexity of the clinical trial empirically not feasible. For example, requesting active-controlled superiority trials might raise the evidence requirements needed for marketing a new drug to prohibitive levels and, in particular, is not a realistic regulatory standard for orphan indications.

Uncertainty linked to the presence of subgroups Towse et al. (2010) also mention the issue of outcome uncertainty among subpopulation as patients might respond differently to a treatment which leads to uncertainty while assessing the efficacy. This was the reason for the UK implementation of the Velcade risk-sharing scheme, whose purpose was to ensure the identification of patients responding to the treatment and was proving for a retrospective reimbursement for patients that did not respond to treatment.

1.3.3.2 Risk-sharing scheme and innovative pricing

Consequences of this uncertainty of reimbursement and patient access to innovative products As the effectiveness of a drug is only known once the drug is on the market, pharmaceutical firms have incentives to overestimate the efficacy of their drug and underestimate the number of patients treated to get the highest price possible for their medicinal product. Post-marketing monitoring of drugs and studies enable health insurers to know the real value of a drug and the volume of demand.

This uncertainty surrounding innovative medicinal products also leads to a delay in reimbursement decisions and patient access. For this reason, payers and manufacturers had made special arrangements with the aim of sharing the financial risk around this uncertainty. Such "managed entry agreement schemes" as they are labelled in the Transparency Directive, which are summarised in the economic literature under the term "risk-sharing agreements" have different features and different names including "price-volume agreements (PVAs), outcome guarantees, coverage with evidence development (CED), and disease management programmes"[55] depending on the uncertainty which is to be tackled.

[55]Cf. EMINET, April 2013, p.15

Implementation of risk-sharing schemes In recent years, an increasing number of member states have been implementing such schemes, in order to control their budget expenditures while providing patients with access to innovative drugs and achieving more value for money.

This is especially the case for biologics and niche medicinal products for unmet medical needs, where the uncertainty around the product´s effectiveness is the highest. These products are very expensive due to the large R&D costs involved and the limited population concerned. This innovative pricing spreads the risk of the existing uncertainty between the health insurer and the pharmaceutical manufacturer. While there exists different typologies, with specific classification and sub-classification, risk-sharing schemes are mainly divided between outcome-based schemes, so-called performance-based risk-sharing schemes, financial risk-sharing schemes, and so-called volume-based risk-sharing schemes. Under a performance-based scheme, the pharmaceutical firm is reimbursed totally or partly only when the effectiveness of the medicinal product is higher than a certain threshold defined ex-ante. A volume-based risk-sharing scheme consists of reimbursing the sales of an innovative medicinal product until a certain volume defined ex-ante in the agreement.

Further area for research: Analysing how risk-sharing schemes can be an instrument to solve information asymmetries (hidden action and hidden information) in pharmaceutical markets Once the different schemes put in place among the member states have been characterised and compared, it is of interest to investigate how risk-sharing schemes - by aligning the price of the medicine with its real world performance - can be used as an instrument to solve hidden action issues and to promote innovation in pharmaceutical markets and remedy hidden information issues concerning the effectiveness of the pharmaceutical product for the health insurer. (Chapter 4)

Chapter 2

ECONOMIC ANALYSIS OF THE DEFINITION OF THE RELEVANT PRODUCT MARKET FOR HUMAN MEDICINAL PRODUCTS IN THE EUROPEAN UNION: A USER'S GUIDE

ABSTRACT OF CHAPTER 2

Defining the relevant market is a key step in mergers and dominance investigations as it enables the identification of market participants. The approach required for pharmaceuticals in defining the relevant market requires taking into account the specifics of the demand substitution patterns on these markets.

The EC bases its analysis on the ATC classification system which reflects the different possible levels of demand substitution patterns and hence the scope of the relevant market.

In order to identify the key criteria which explain the choice of a broad or a narrow market definition, and whether the EC tends to narrow the scope of the relevant market in time, a logit model will be used to investigate the criteria employed in defining the relevant product market in pharmaceutical merger decisions from 1989 to 2011.

Results show that demand-side substitution patterns are the basis upon which the relevant product market may be defined while supply-side criteria, political and economic variables do not play role. The intended use of a product is the main substitution criterion together with efficacy, channel mode, and prescription status of the product. The results confirm that the EC has tended since 2004 to decrease the scope of the relevant market to very narrow markets at the molecule level, mainly based on channel mode, galenic form of the product, or its active ingredient.

The relevant market contains different economic markets with products being perfect or quasi perfect substitutes. The boundaries of the relevant market hence offer the smallest possible market that a firm can monopolize. The relevant market can be defined:

"so as to encompass all these products or services which are considered to be effective substitutes for the products or services at the centre of investigation"[1].

According to Scherer (1990, p. 73), an ideal market definition would take into account not only demand-side substitution, but also supply-side substitution patterns. In his definition, firms producing non-substitutable products can become competitors if they can switch between products easily without significant additional costs or risks following a small but permanent increase in prices. This is the case when firms use the same production factors, for example the same skills and equipment.

The relevant market has two components, one geographic and one product market. The relevant market results from the combination of these two components. Once the definition of the relevant product market has been reviewed and applied to pharmaceutical markets (2.1), an econometric analysis of the relevant product definitions performed by the EC in its merger decisions from 1989 to 2011 is carried out with the aim to list the different criteria applied to define the scope of the relevant market (2.2).

2.1 The relevant product market and its application to pharmaceuticals

The rationale and principles of the relevant product market are analysed at first (2.1.1). Then, the approach of the EC and national competition authorities is reviewed (2.1.2). Finally, the relevant criteria are listed and explained (2.1.3).

2.1.1 Rationale and principles for market definition

Once the rationale of the definition of the relevant product market has been investigated (2.1.1.1), principles behind the concept are analysed (2.1.1.2). Ultimately, the issue is raised whether a unique relevant product market can be defined in both merger and dominance cases (2.1.1.3).

2.1.1.1 Rationale of the relevant product market

European competition legislation The concept of the relevant market is closely linked to the objectives of the EU Competition Policy. Consequently, the Directorate General for Competition of the EC

[1] Cf. Bishop S., Walker M., 2002, p.82

stresses that:

> "Competition policy is about applying rules to make sure that businesses and companies compete fairly with each other. It has many positive effects:
>
> -encouraging enterprise and efficiency
>
> -widening consumer choice
>
> -helping deliver lower prices and higher quality."[2]

The European competition legislation is included in the articles 101-110 of the Treaty on the Functioning of the European Union[3] (hereinafter TFEU) and the European Community Merger Regulation[4] (hereinafter ECMR). The EC is responsible for enforcing European competition legislation.

The exercise of market power is a key concern for antitrust authorities. Hence, the article 102 of the TFEU deals with abuse of dominant position and prohibits dominant firms from abusing their market position. It states that:

> "Any abuse by one or more undertakings of a dominant position within the common market or in a substantial part of it shall be prohibited as incompatible with the common market insofar as it may affect trade between member states".

Similarly, article 2(3) of the ECMR states that:

> "A concentration which would significantly impede effective competition, in the common market or in a substantial part of it, in particular as a result of the creation or strengthening of a dominant position, shall be declared incompatible with the common market".

Market definition and market power In a Structure-Market-Conduct Paradigm derived from the neoclassical analysis of markets according to the Harvard school of thought, the performance of a market is deemed to be influenced by the buyer's and seller's conduct which in turn depends on the structure of the relevant market.

In EU community law, very large market shares, such as over 50%, raises the presumption that a firm is dominant (Hoffman-La Roche 1979). The pharmaceutical company Hoffmann-La Roche was found to have a dominant position in markets for certain vitamins and to have abused its position by entering

[2] Cf. Directorate General for Competition Homepage, http://ec.europa.eu/competition/index_en.html, last accessed August 2013.

[3] Available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2008:115:0047:0199:en:PDF, last accessed February 2011.

[4] Available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32004R0139:en:NOT, last accessed February 2011.

into exclusive agreements, or agreements containing exclusionary loyalty rebates with purchasers. This practice of defining the market in order to decide on the market power was upheld by the courts[5].

In dominance investigations (art. 102 TFEU), the definition of the relevant market is an important preliminary step as it aims at defining the substitutability of products or services to be considered as representing an effective competitive constraint on the products or services under investigation. Article 102 prohibits an abuse of dominant position if the undertaking concerned is dominant. Therefore, if the market is defined too narrowly, the market shares of the products under investigation are likely to be overestimated and the company considered as dominant within the market. On the other hand, if the market is defined too broadly, then the market shares of the products under investigation will be underestimated, thus the firm involved is likely to be found not dominant within the market.

In merger controls, defining ex-ante the market boundaries aims at calculating market shares and assessing the competitive situation after the merger, in order to predict whether the merging firms will have incentives and capabilities to impede competition within the market concerned either by unilateral or coordinated effects (Bishop and Walker, 2010). Unilateral effects correspond to the creation or the strengthening of a dominant position by the elimination of a competitor while coordinated effects correspond to the creation or the strengthening of a collective dominant position which increases the likelihood that the firms involved are able to coordinate their behaviour and raise prices. Coordinated behaviour may occur even when the firms do not properly enter into an agreement within the meaning of article 101 TFEU. In merger control, a narrow market definition decreases the likeliness of the merging firms to have overlapping products while a broader market definition increases it.

2.1.1.2 Principles of market definition

The EC released guidelines to provide guidance on the application by the EC of the concept of relevant market in its enforcement of European community law.

The definition of the relevant product market provided for in this Commission notice insists on the demand-side substitutability as:

"A relevant product market comprises all these products and/or services which are regarded as interchangeable or substitutable by the consumer, by reason of the products' characteristics, their prices and their intended use". (Commission notice, par. 7)

While giving more importance to demand-substitution patterns, the Commission notice stresses that the competitive constraints a firm faces consist of a combination of the demand-substitution (a), the supply-side substitution (b) and the potential competition (c).

[5]Cf. Case 6/72 Continental Can Co Inc. (1973), ECR 215.

(a) Demand-side substitution Demand-side substitution constitutes the most immediate competitive constraint as the products considered are in direct competition.

Demand-side competition criteria mentioned in the Commission Notice include:

- the functional substitutability between products,
- the use and characteristics of products,
- the consumers preferences,
- the existing barriers and costs limiting substitution,
- as well as quantitative criteria and price differences between products (Navarro et al., p. 97 -107).

Demand-side substitution is assessed by applying a "Small but Significant and Non-transitory Increase in Price" test (hereinafter SSNIP) also called a hypothetical monopolist test (Bishop and Walker, 2010). This test aims at identifying the smallest set of products, producers and geographical regions where a hypothetical monopolist would be able to increase its profits by applying a small but significant and permanent increase in price over the competitive level. The level of the price change is interpreted pragmatically by the competition authorities. In practice, it corresponds to a 5% or 10% increase in price. The SSNIP test approach is at the heart of the Commission notice on market definition.

The SSNIP test was first applied in the US as it is mentioned in the US Horizontal Merger Guidelines since 1982[6]. It

> "requires that a hypothetical profit-maximizing firm, not subject to price regulation, that was the only present and future seller of these products ("hypothetical monopolist") likely would impose at least a small but significant and non-transitory increase in price ("SSNIP") on at least one product in the market, including at least one product sold by one of the merging firms". (US Horizontal Merger Guidelines 2010, para 4.1)

To apply the SSNIP test in practice, competition authorities start the investigation with the smallest possible market and investigate whether a 5% price increase is profitable for the firm. If this is not the case, then the firm does not have enough market power to raise prices. The test is repeated by adding the next closest substitute until a 5% price increase becomes profitable for the firm. All products taken into account in the test constitute the relevant market.

[6]Cf. US Horizontal Merger Guidelines 2010, US Department of Justice and Federal Trade Commission, http://www.ftc.gov/os/2010/08/100819hmg.pdf, last accessed February 2011.

Application of the SSNIP test in pharmaceutical markets Because of the multitude of stakeholders involved and their various interactions, the role played by prescribing physicians and reimbursement by health insurers, the assumptions underpinning the SSNIP test are not straightforward to apply to pharmaceuticals. The SSNIP test investigates how consumers will react to a small but not transitory increase in prices. However, patients do not choose the pharmaceutical they consume as it is prescribed by their physician and they do not bear the full price of the pharmaceutical. Pricing of pharmaceuticals is also constrained meaning that non-price competition (quality, innovation...) plays an important role in consumer choice.

While demand-substitutability is the most immediate constraint on a supplier, other competitive constraints which are less immediate for the firms, such as supply-substitutability and potential competition, also have to be considered when defining the relevant market and tend to widen it.

(b) Supply-side substitution patterns The investigation of supply-side substitution patterns completes the analysis of demand-substitution patterns when the substitution can be considered as immediate. Here, the EC indicates that, in general, it does not take into account supply substitution except when "its effects are equivalent to these of demand-substitution in terms of effectiveness and immediacy" (Commission notice, par. 20).

Supply-side substitution exists when firms are able to make a short-term switch in their production to manufacture the product under investigation without bearing "significant additional costs or risks" (Commission notice, par. 20) following a small and non-transitory increase in prices. Such "additional costs" are referred to in the Commission notice (par. 23) as the adjustment of tangible and intangible assets, additional investments or time delays. For example, in the case of paper manufacturing, while one paper plant manufactures a paper of a given quality, it can switch to a paper of a different quality quite rapidly without incurring significant additional costs. The effects of supply-side substitution arise from the demand substitution patterns as in the case of a price increase, if a firm switches its production, some consumers will switch to the new firm manufacturing the product in question which is immediately available (Navarro et al., p. 115). Significant costs would exist if barriers to entry are present in a market, such as with patents protecting a product or a production process. The presence of supply-side substitution patterns tends to widen the market.

(c) Potential competition The last source of competitive constraint for firms which has an impact on the relevant market is potential competition. The Commission notice stresses that potential competition is to be examined at later stages of the investigation as it depends on conditions of entry into

the market (Commission notice, par. 24). Potential competition is taken into account once the relevant market has been defined and competition concerns may arise.

To assess potential competition, the EC investigates whether new competitors can easily enter the market in the short-term and are able to counteract the effect of the concentration and limit the ability of the merging firm to have market power. It is of interest to the scope of the relevant market when the market entry of potential competitors can happen within a short period of time, is likely, and would provide competition in the relevant market under examination. When this is the case, the EC considers diverse factors such as the presence of potential competitors, hints indicating that they are willing to enter the market and the risks of failure or success doing so (Navarro et al., p. 241-260). While supply-side substitution is used to identify market participants and to calculate market shares, potential competition is only considered at the assessment stage. It is used to determine whether it may or may not prevent the strengthening or the creation of a dominant position within the market under investigation.

2.1.1.3 A unique relevant market in mergers and dominance investigations?

The terminology used when defining the market suggests that the result of the analysis is an invariant fact (Evans, 2010). It is however the result of a process in place to identify the competitive constraints faced by a firm.

The definition of the relevant market essentially depends on the objectives pursued (Philippe, 1998, p.126). When for example the reference point in time is different, the analysis and the result of the analysis might differ as the determination of the relevant market is "facts-intensive" (Morse, 2003, p. 656). Therefore, "the relevant market cannot be defined in isolation from the agreement or practice under consideration" (EFPIA, 2004).

Demand-side and supply-side substitution patterns are observed in dominance investigation cases yet they are expected and assessed in merger investigations. Potential competition can be omitted in dominance cases.

Defining the relevant market in dominance cases While the relevant market is defined ex-ante in merger cases, to assess the effects of a merger in the product market concerned, the relevant market is defined ex-post in dominance investigation cases.

In dominance investigation cases, the aim is to reconstitute ex-post how the relevant market has been constituted, over a given period of time, where firms had market power. Substitution patterns can thus be observed and measured. When applying the SSNIP test, the alleged dominant firm may be already pricing above the competitive price thus the analysis should be done carefully while processing price variations.

Defining the relevant market in merger cases In merger cases, merging firms' starting situation as well as their competitive constraints are observable for the competition authorities who have to investigate how the situation might evolve after the merger based on past data. In that regard, dynamic analysis is one part of the market definition as future products may provide genuine competition.

2.1.2 Approach on the relevant product market for pharmaceuticals

In the majority of cases dealing with pharmaceuticals, the market definition takes place during merger controls. Based on the Commission notice, the EC investigation involves different steps. Its approach on the definition of the relevant market can be easily and regularly observed and analysed in mergers decisions. Hence, the exercise of market definition by national competition authorities follows the EC's approach quite closely (Siebert and Priest, 2007, p.148).

The conduct of market investigation will be analysed at first (2.1.2.1) and the use of the ATC classification described (2.1.2.2). Then, the approach in terms of potential competition will be further examined (2.1.2.3) and some critics will be drawn (2.1.2.4).

2.1.2.1 The conduct of market investigation

Identification of the market players and of the affected markets Questionnaires are an important way for the EC to gain knowledge of the market and to gather the opinion of the competitors involved and their customers, in general intermediate customers. The questions asked vary according to the markets and the firms concerned, as well as the needs of the EC with regards to the issues at stake. However, the general framework of the questionnaire remains the same.

The first step in market investigation is to identify the firms involved and the scope of their activities. The second consists of defining the affected markets and their products and geographic dimensions, in order to assess competitiveness. To this purpose, questionnaires are sent to both the competitors and customers as defined in the previous step. Each questionnaire has to be completed in a confidential and a non-confidential version.

With regard to the questionnaire addressed to the competitors, the first part is dedicated to the identification of the firm (name, active country, turn-over within a specific market segment, market shares...). This part aims to discover the importance and the role played by the firm in the market under investigation. The second part examines the definition of the relevant product market under investigation. One key question concerns the identification, by the firm, of competing products. Through this question, the EC aims to confirm its knowledge of the market. Another key question is related to the most appropriate

definition. In reference to a specific classification for medicines, the so-called ATC classification system [7] which was developed by the EphMRA[8], firms are asked to provide which market definition they consider as the most accurate and to briefly justify their choice.

Performing the SSNIP test in the market investigation The objective behind the definition of the relevant market is to assess market power. To that purpose, the SSNIP test is implemented in order to identify the competitive constraints that the competitors exerce on each other. Therefore, in one specific question the competitor is asked whether it considers the products manufactured and/or sold by the merging firms as substitutable (i.e. interchangeable) and whether a 10% increase in price for the product concerned would be profitable for the merging firms. In case the answer is positive, it results that the products under investigation do not exerce a significant competitive constraint on each other so that they constitute different markets. Otherwise, a negative answer means that the products under investigation belong to the same relevant market. The SSNIP test will continue by considering a wider market until a separate market has been identified.

In the questionnaire for customers, the SSNIP is formulated so that the customers have to answer whether they consider the products are interchangeable and whether, in case of a price increase, they would switch to another manufacturer. This question aims specifically at recognising alternatives of the products on the market and indirectly provides a hint of the relevant market definition based on the customer's opinion.

The following questions investigate further as they specifically ask about the closest competitors of the firms involved and, if relevant, whether generics can be considered as valid alternatives. Even if generics are considered by their intrinsic qualities as the closest competitors of an originator product, the question of the validity of generics as an alternative shows the care taken by the EC to fully understand the reality of the market under investigation.

Tackling the potential competition After the static questions, aimed at defining the structure of the market, dynamic questions are asked in order to assess the potential entrants in the market. These questions examine the existence and the likely effects of pipeline products, and whether other pipeline products are expected in the near future.

Finally, the presence of barriers to entry is investigated. Barriers to entry refer to the existing barriers due to regulation, distribution, brand, reputation or R&D. In this section of the questionnaire, a control question is always added to check the validity and the logic of the answers provided.

[7] Cf. EPHMRA Anatomical Classification Guidelines 2010, available at http://www.ephmra.org/PDF/ATC%20Guidelines%202010.pdf, last accessed February 2011.
[8] Cf. http://www.ephmra.org/.

2.1.2.2 Use of the ATC classification

With regards to the product market definition, the ATC classification system, as already mentioned, is used as a starting-point.

Using the ATC level 3 as a starting point In the EU's market definition investigation, the EC takes as a general rule the ATC level 3 as a starting point for its analysis of the relevant market.

In the case 85/76 Hoffmann-La Roche vs. Commission, the ECJ stated that:

> "the concept of the relevant market in fact implies that there can be effective competition between the products which form part of it and that presupposes that there is a sufficient degree of interchangeability between all the products forming part of the same market in so far as a specific use of such products is concerned".[9]

At the third level, medicinal products are grouped by their therapeutic indication i.e. intended use[10]. The therapeutic use of a medicine is the base level to analyse the demand substitution patterns of the products as they may be interchangeable from a therapeutic point of view.

Relevance of other ATC levels due to demand-side substitution patterns An investigation of the substitution patterns at other ATC levels may be relevant in specific cases depending on the medicines or the indication concerned, for example, when medicinal products at the ATC level 3 have different indications or when the competitive constraints of the undertakings involved are faced at another ATC level than the level 3, such as when the demand substitution patterns exist at a narrower level.

Hence, the investigation has to be performed at a narrower level, either at the ATC level 4 or even ATC level 5. This is particularly true when the ATC 3 category contains old and new generation molecules[11]. In the case COMP/M.5253 Sanofi-Aventis/Zentiva[12], the EC stated that an analysis of the relevant product market at the molecule level is relevant in three particular situations:

1. When prescribing doctors are required by legislation to use the INN of the molecule,
2. When drugs are reimbursed according to the price of the generic version due to regulatory rules,
3. When pharmacists are required by delivery to substitute the originator medicines with its generic version

[9] Hoffmann-La Roche vs. Commission, case 85/76, 1979, par.28, http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:61976J0085:EN:PDF.
[10] Cf. Case COMP/M.5295 Teva/Barr, recital 11.
[11] Cf. case COMP/M.5253 Sanofi-Aventis/Zentiva.
[12] Cf. case COMP/M.5253 Sanofi-Aventis-Zentiva, recital 18

Further to the criteria mentioned above, the analysis may also differ from the ATC level 3 classification when the ATC level 3 contains heterogeneous medicinal products.

Thus, in the case COMP/M.5253 Sanofi-Aventis/Zentiva, the EC investigated the market for fluoro-quinolones that are synthetic broadspectrum antibiotics. At ATC level 3, fluoro-quinolones differ between old and new generation molecules. While both molecules have the same subset of indications, they differ in their galenic form. A relevant product market for oral fluoro-quinolones and one for injectable quinolones were defined by the EC due to the specific demand-side substitution patterns. As a result of the differences in the galenic form, a distinct demand exists for hospital markets and for pharmacy markets. Because of the medical conditions of hospital patients, the injectable form may sometimes be the only form that can be administered to hospital patients. As a consequence, there is only a limited medical substitution between these forms with regards to the preferred situation in which they are employed. This analysis of the demand-side substitution patterns was reinforced by the analysis of supply-side substitution patterns, as the EC also stressed the limited supply-side substitutability in the manufacturing process of the different galenic forms which have few steps in common, hence limiting the supply-side substitutability.

Supply-side substitution patterns and generics in the choice of the ATC level As mentioned previously, supply-side substitution patterns are also important to motivate the choice of other ATC levels. Conditions regarding the market entry on the supply-side are an important way to refine the scope of the relevant market. The analysis of supply-side substitution patterns is considered as an additional indicator, supplementing the investigation of demand-side substitution patterns.

The context of generic medicines is particular. As mentioned in the first chapter, when the patent of an originator product has expired, it can be copied by generic manufacturers who do not have to undertake research and hence can price their generic version at the marginal cost. In the case COMP/M.5865 Teva/Ratiopharm, the EC stressed that market entry within a short period of time could happen in very restrictive cases, when the following criteria are met:

> "(i) the competitor already had the same pharmaceutical form and dosage of the target product in another market within the European Economic Area (EEA), and especially in neighbouring markets to the target market;
>
> (ii) the competitor already had a significant base of generic operations with a number of products in the target market, belonging to the same or closely related therapeutic areas; and
>
> (iii) the competitor had no specific economic disincentive to introduce the product, such as a risk of cannibalizing existing sales of another product." (Case COMP/M.5865, recital 56)

In the case COMP/M.4314 Johnson & Johnson/Pfizer Consumer Healthcare, the EC analysed the market

for nicotine replacement therapies (hereinafter NRT). Three main types of NRT exist: nicotine patches (1), nicotine gums (2), nicotine lozenges (3). Contrary to other forms, transdermal patches release over a long period of time a certain amount of drug which leads to an increase of the therapeutic efficiency of the product and a decrease of side effects.

The market investigation concluded that NRT patches constituted a separate relevant market because of different customer preferences. The EC also decided to separate the market between manufacturing and direct-sale of nicotine patches from other transdermal patches. Two reasons were stressed relating to the supply-side specifics of the patches. The first, is the absence of supply-side substitutability because the producers of other transdermal patches cannot manufacture nicotine patches in the short term without incurring significant initial costs. Secondly, non-supply side substitutability is related to the fact that nicotine patches are protected by patents so that generic manufacturers cannot impose a competitive constraint.

Relying only on the ATC classification would be inappropriate. The ATC classification is considered as the starting point for the definition of the relevant product market. The General Court in the AstraZeneca AB v EC[13] stated that market definition should focus on the review of the products which are seen as interchangeable by the consumers because of their price and intended use notwithstanding the ATC category (Westin, 2011, p.60).

Returning to the concept of the relevant market definition, it has been shown that it is primarily based upon demand-substitution patterns, and can be complemented by supply-side substitution patterns and future substitution patterns. The application of the relevant market definition to pharmaceuticals requires taking into account the specifics of pharmaceutical markets and necessitates some adaptation and special measures.

Special case: Use of the EDMA classification for diagnostics

Definition of diagnostics The ATC classification is a system for medicinal products. However, mergers increasingly involve diagnostic technologies. Diagnostics, which are increasingly used in accordance with more personalised medicines correspond to "tests performed on biological samples to diagnose or rule out a disease".[14]

Diagnostics can either be performed in clinical laboratories, or used by patients through simple self-tests. Two types of diagnostics exist, the in-vivo and in-vitro diagnostics (hereinafter "IVD").

[13] Cf. AstraZeneca AB v European Commission, T-321/05

[14] Definition of the European Diagnostics Manufacturer Association, available at http://www.edma-ivd.be/, last accessed February 2011.

While in-vivo diagnostics consist of experimentation using the whole living human-being (such as radiocontrast agents used to improve the visibility for X-ray based imaging or magnetic resonance imaging), IVD corresponds with an experiment using components of an organism such as a medical device used to perform assays in a glass tube. In-vitro diagnostics are defined in the EU as:

> "Any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:
>
> - concerning a physiological or pathological state, or
> - concerning a congenital abnormality, or
> - to determine the safety and compatibility with potential recipients, or
> - to monitor therapeutic measures." (Dir. 98/79/EC, Art.1, par. 2.b)

The IVD industry is developing as it provides patients, hospitals and health insurers with clear benefits by enabling earlier and more appropriate treatments, decreasing the length of stay in hospitals, and reducing the costs of treatment. They are particularly used for diabetes, AIDS, and turberculosis treatments.

IVD systems are made of reagents, instruments, and accessories which form a system. The EC found that competition in the IVD market was mainly based upon securing the sales of reagents which are liquids used to perform tests[15] as most instruments and accessories can be used for several tests with different specific reagents. However, some IVD manufacturers can market closed systems meaning that an instrument can only be used with their reagents. This should be assessed on a case-by-case basis.

In case No IV/M.950 Hoffmann La Roche/Boehringer Mannheim, it appears that, from a technical point of view, even in closed systems, reagents from a certain supplier can be used with an instrument from another provider, though it does require a certain know-how and time investment[16].

Using the EDMA classification to define the scope of the relevant market An increasing number of merger cases involve diagnostics manufacturers. The ATC classification does not cover IVDs so that the EC uses to define the relevant market the one of the European Diagnostics Manufacturers Association (hereinafter "EDMA").

The EDMA IV classification is a special product classification scheme for IVD which functions as the ATC system. In its 2011 version, it contains four levels. In the first category, it differentiates between

[15] Cf. case No IV/M.950 - Hoffmann La Roche/Boehringer Mannheim, recital 30
[16] Cf. case No IV/M.950 - Hoffmann La Roche/Boehringer Mannheim, recital 31

Clinical Chemistry, Immunochemistry, Haematology, Microbiology - Culture, Infectious Immunology, Genetic Testing, and Instruments, Spare parts, Service, Software[17]. Each category is then subdivided into three further narrower subcategories.

In the case IV/M.950 Hoffmann La Roche/Boehringer Mannheim, the EC found that the second level of the EDMA classification was relevant to define the product market based on two main testing technologies (protein based tests and DNA probes also called molecular products). In the case M.5661 Abbott/Solvay Pharmaceuticals, the EC market investigation concluded that there was a possible separate market definition for molecular products [18].

2.1.2.3 Approach in terms of potential competition

As mentioned previously, the approach regarding the relevant product market definition changes whether it is used for dominance investigations or mergers. In the former instance, a dynamic approach has to be adopted in order to investigate the existence of a possible "pipeline competition" which would change the market definition.

Dynamic analysis and investigation of pipeline competition Besides the medicinal products having already been granted marketing authorisation, pipeline products can be defined as products that are not on the market yet, but which are at an advanced stage of development.

The EC considers as "pipeline products", potentially impacting the competitive situation of merging firms, products which are at phase III of their clinical trials. In the case COMP/M.737 Ciba-Geigy/Sandoz, the EC justified its choice of taking only products in phase III onwards as representatives of the pipeline competition by explaining that in phases I and II of clinical trials, the chances of being later successfully marketed were 10% and 30% respectively, which increased to 50% for projects in phase III. The development process for medicines is very cumbersome and failures happen at each stage, with decreasing probability.

Consequently, potential future medicinal products at an early stage of development are considered as having no impact on the market because of their very low probability of being marketed.

Approach in terms of downstream markets In its approach on future markets, the EC assesses the competitive impact of mergers on innovation by focusing on downstream markets and the likely effects of the mergers on prices and output.

[17]Cf. EDMA 2011 classification, available at http://www.edma-ivd.be/index.php?id=882, last accessed February 2011.
[18]Cf. Case No COMP/M.5661 - Abbott/ Solvay Pharmaceuticals, recital 21.

The approach in terms of "potential competition" was initially used in the US and has "traditionally been invoked (...) when a merger reduces the number of entrants who could discipline competition in markets in which they do not currently compete" (Rapp, 1995, p.39).

This approach in terms of potential competition intervenes in the competition assessment, not in the definition of the relevant market. In the case COMP/M.555 Glaxo PLC/ Wellcome PLC, the EC investigated the potential competition as it expressly took into account the effect of the merger on the development of future competition (Landman, 1998). In its investigation, the EC found that both merging firms were undertaking research in the field of antimigraine drugs and were both simultaneously undertaking clinical trials. Wellcome's product was in phase III of clinical trials leading the EC to express some concerns regarding the competitive situation within the market for antimigraine drugs after the merger. To this purpose, Glaxo voluntarily accepted to grant an exclusive license to a third party to undertake the development and the marketing of its future antimigraine medicinal product.

2.1.2.4 Weaknesses of the analysis of market definition by the European Commission

A case-by-case approach focusing on generic substitution : As defined in the Commission notice for defining the relevant market and the use of the SSNIP test, the EC's approach focuses primarily on the demand-substitutability with its instrument, the SSNIP test. By applying the SSNIP test, the EC does not offer any criteria to define whether and, if applicable, how the SSNIP test should be applied to pharmaceutical markets.

Hence, it is essential to have an appropriate knowledge of the specific market concerned before beginning the investigation. Taking a closer look at the US and having reviewed recent antitrust enforcement action by the F.T.C in the US, Morse (2003) listed some criteria used by competition authorities to define the scope of the relevant product market for pharmaceuticals. The criteria mentioned are:

> "(1) whether drugs treat the same disease, condition, or indication;
>
> (2) whether drugs treat a disease by interacting with the body in the same manner (i.e., whether they have the same "mechanism of action");
>
> (3) whether drugs have the same specific chemical compounds;
>
> (4) whether drugs have the same dosage form such as injectable, liquid, capsule, tablets, or topical;
>
> (5) whether drugs have the same frequency of dosage, such as once-a-day or extended release;
>
> (6) whether drugs have the same strength of dosage, distinguishing, for example, 30mg and

60mg tablets;

(7) whether drugs are branded or generic;

(8) whether drugs require a prescription or are sold over-the-counter; and

(9) whether drugs are currently marketed or are in development" (Morse, 2003, pp.643-644).

The list of criteria looks like an anthology that is hardly ready to be used by competition authorities. An important issue concerns the ranking among the criteria listed. Thus, the EC approach lacks precise principles for substitution patterns with differentiated products where degrees of interchangeability and cross-elasticity vary among products and therapeutic areas.

Demand substitutability is not only therapeutic but also economic in pharmaceutical markets as, in the end, the final payers are the public health insurers who can restrict access to certain cost-ineffective medicines which would lead to a restriction in the substitutability between products. These economic patterns, present within pharmaceutical markets are not listed in Morse's criteria. Their importance in the substitutability patterns is somehow increasing due to the national cost-containment approaches and the difficulties met by the pharmaceutical companies to gain market access.

Different dynamic approaches The EC assesses the competitive impact of mergers on innovation through a dynamic approach of pipeline products. It focuses on downstream markets, meaning on the likely effects of mergers on prices and output. Taking into account potential markets is important because competition among pharmaceutical products is present not only at the level of the sales but also at the R&D stage, in order to discover a new active pharmaceutical ingredient (hereinafter API) or a new formulation. The future market approach of the EC is one main approach among three which are used to incorporate dynamic efficiency in the assessment of mergers (Morgan, 2001, p.183).

The first basic approach, called the "conventional framework" consists of investigating the current market and taking into consideration markets where merging firms are in competition for licensing similar technologies. Like the EC's future market approach, the "conventional framework" approach deals with the potential effects of mergers on downstream markets competition.

The second approach is that of "innovation markets", which shifts the focus from future prices and output instead onto R&D competition. This is this approach which is currently in place in the US where antitrust authorities analyse the effects of mergers in terms of innovation markets and hence consider R&D markets as separate from product markets. Referring to Solow's growth theory that insists on the importance of the total factor productivity, explained by exogenous technical progress, Gilbert and Sunshine (1995) highlight the importance of R&D for the path of industrial innovation. Noting that traditional merger enforcement is limited to product markets and hence fails to take into account innovation

efforts and incentives, they advocate in favour of a dynamic analysis of mergers projects, especially in high-technology industries where innovation represents an essential factor of non-price competition and welfare gains.

The concept of innovation markets was first introduced in the US in the "Antitrust Guidelines for the Licensing of Intellectual Property" (Intellectual Property Guidelines)[19]. Guidelines provide that:

> "An innovation market consists of the research and development directed to particular new or improved goods or processes, and the close substitutes for that research and development". (Antitrust Guidelines, par. 3.2.3)

Considering that competition in R&D would enhance innovation of new processes and products and that a merger hampering the innovation path should be prohibited, an analysis in terms of innovation markets should be undertaken. More precisely, innovation markets are considered in a merger or a joint-venture as "a set of activities and a geographical area in which a hypothetical monopolist would impose at least a small but significant and non-transitory reduction in R&D effort" (Gilbert and Sunshine, 1995, p. 594). Similar with the SSNIP test in the definition of the relevant product market and presuming a worldwide relevant geographic market, the ability and the incentives of a firm to cut back its R&D investment are a sign of its market power in this relevant innovation market. The elimination of competition in R&D would indeed decrease innovation and harm consumers.

The aim of such an approach is to consider R&D as an input for the production of final goods and services. Such an approach should however be limited to situations where merging firms undertake R&D with specific assets (Rapp, 1995). The specificity of these assets is that competitors cannot compete to own them. If the asset is not specific, there is no barrier to entry, and hence entry into R&D markets would be easy and the innovation market would be competitive. For Gilbert and Sunshine (1995), the notion of innovation market entails three issues. Firstly, the ability of the merged firm to decrease its R&D spending shall be assessed through the investigation of its control of total R&D's assets as well as the feasibility to sustain collusion with other firms. Secondly, its incentives to do so shall be analysed as it varies according to the actual and potential competitive downstream market. Finally, the impact of the merger for the efficiency of the R&D investment has to be considered. It depends essentially on whether the merged firms own complementary assets required to innovate.

More precisely in the case of mergers or joint-ventures, innovation markets can be defined as "a set of activities and a geographical area in which a hypothetical monopolist would impose at least a small but

[19]Cf. Antitrust Guidelines for the Licensing of Intellectual Property issued by the US Department of Justice and the Federal Trade Commission, 6 April 1995, Part 3 "Antitrust concerns and modes of analysis", http://www.justice.gov/atr/public/guidelines/0558.htm#t323, last accessed February 2011.

significant and non-transitory reduction in R&D effort" (Gilbert and Sunshine, 1995, p. 594).

The five steps underlining the innovation markets approach Gilbert and Sunshine (p. 595) explain that the innovation market approach requires five steps to be completed.

First, the overlapping R&D activities between merging firms must be defined. The second step consists in identifying the main innovation sources, by focusing on existing and potential specialised assets which are considered as key elements in the innovation process. In the third step, the actual and potential competition on downstream products is investigated, whilst in the fourth step, the impact of the post-merger concentration on R&D investment has to be assessed. Finally, in the last step, R&D efficiencies created by the merger are evaluated by taking into account complementary R&D assets, as well as the economies of scale in R&D, leading to the elimination of redundant programs.

During the investigation, the ability of the merging firms and their incentives to decrease their R&D spending depending on the actual and potential competitive downstream markets are taken into consideration. The impact of the merger for the efficiency of the R&D investment is also important, as it depends essentially on whether the merging firms both own complementary assets.

Comparison innovation markets and future market approach For its part, the EC studies future market developments as a part of the product market it analyses as applied in the case COMP/M.737 Ciba-Geigy/Sandoz (Landman, 1998). The aim of this dynamic analysis is to promote innovation and protect future competition on new products. It is useful especially in cases where the relevant market is concentrated and that dominant firms can control prices and output, and secondly where there are barriers to entry or where potential competitors are scarce. The EC insisted that it was not following the innovation market approach as "research and development cannot as a rule be traded between pharmaceutical companies" (Case COMP/M.737, recital 42).

The merger case Glaxo PLC/Wellcome PLC was investigated both by the Federal Trade Commission (hereinafter FTC) and the EC, and enables a comparative analysis of both approaches of pipeline competition. In the case COMP/M.555 Glaxo PLC/ Wellcome PLC, the EC clearly took into account the effect of the merger project on the development of future competition (Landman, 1998). The EC noted at first that both merging firms were undertaking research in the field of the antimigraine drugs and were both in clinical trials. Wellcome's product, in particular, was in phase III of the clinical trials. Therefore, Glaxo voluntarily accepted to grant an exclusive license to a third party to undertake the development and the marketing of this future product. However, as some other companies had R&D projects at similar stages as the one of Wellcome, it concluded that the effects of the merger on potential competition were limited

only.

As a comparison, the FTC's analysis was based on a different market definition than the one defined by the EC. It focused its analysis on the R&D market for oral antimigraine treatment. Starting from this market definition, the FTC found that the merger would increase Glaxo´s incentives to unilaterally reduce output on the defined R&D market. Accordingly, it required Glaxo to divest its worldwide relevant assets for oral antimigraine development projects and to ensure that the acquirer could successfully take them over (Landman, 1998). Interestingly, without using the notion of innovation market, the EC reached almost the same conclusions as the US anti-trust authorities even though in its potential competition approach it is more likely to consider potential R&D benefits of a merger (Temple, 1997).

One can predict that future developments of the innovation market analysis in the US would surely have an impact on the methodology adopted by the EC for its investigation of mergers effects on future products and market developments. For the proponents of the innovation market approach, post-merger innovation and competition cannot be ensured if innovation efforts are not properly investigated through separate innovation markets. In this approach, R&D is fully considered as an input for the production of final goods and services. However, the innovation markets approach induces that the concrete efficiencies brought by mergers are weighted against speculative future returns of protecting innovation (Morgan, 2001, p.184).

As a result, the future markets approach should rigorously be restricted to situations involving specific assets meaning that competitors cannot compete to own them. In the case of non-specific assets, no barrier to entry exists leading the innovation market to be competitive (Rapp, 1995)

2.1.3 Review of the competition authorities' criteria for market definition purposes

In order to define a first step for the scope of the relevant market within the ATC classification, the EC and national competition authorities justify their choice of taking into account the demand-side substitution patterns by diverse specific criteria which differentiate medicinal products and have an impact on the demand side. Demand-substitution patterns on pharmaceutical markets mainly correspond to therapeutic substitution as explained earlier, as it represents the main criterion to define the interchangeability between different medicines (Westin, 2011, p. 149).

Therapeutic substitution corresponds to ATC level 3 which is the basis of the EC's approach to define the relevant market. However, competition authorities may find that this level does not correspond to the relevant level to define the substitution between pharmaceuticals so that demand side competition

patterns and competitive constraints are located at other levels in the ATC classification and that other criteria would be more appropriate. Moreover, the ATC level 3 may in some cases regroup medicinal products with different therapeutic indications so that a narrower market definition on a case-by-case basis is more appropriate (Siebert and Priest, 2007, p. 149).

Even if defining the relevant market is "intensely factual" (Morse, 2003, p. 634), different criteria in the EC merger decisions are used to take into account the dynamics of competition. These factors are most common to all pharmaceutical merger cases and have been studied and discussed in papers and articles, most exclusively from a legal point of view (Morse, 2003; CRA, 2006; Siebert and Priest, 2007; Westin, 2011). The existing literature focuses on the legal aspects and does not undertake a review of the substitution patterns. Three main substitution patterns explaining the competition authorities' actions can be analysed and are of interest from an economic point of view: competition status (2,1.3.1), prescription status (2.1.3.2), and means of distribution (2.1.3.3).

2.1.3.1 Distinction by competition status: originators/generics

Bioequivalence as a key criterion The competition status criterion is based upon the intellectual property status within APIs, meaning the originator product and its generic equivalents[20]. This distinction by competition status covers the perimeter of the EC's sector inquiry of July 2009.

While the name, packaging and appearance change in comparison to the reference medicinal product, a generic medicine contains the same quantity of active substance as the reference medicinal product. The key factor regarding a generic is the establishment of its bioequivalence meaning that "the generic medicine and the originator product demonstrate essentially the same rate and extent of biological availability of the active substance in the body when administered in the same dose" [21].

The generic version is equally efficient and safe and can be considered as substitutable from a demand-side to the reference product. Once the bioequivalence is provided, generic medicines can be considered as the closest competitor to their originator product. This is the reason why in most European countries generic substitution is not only allowed, but also promoted.

While generic medicinal products are less expensive than their comparative originator medicine, because only manufacturing capabilities are required unlike the originator products which were the result of R&D activities, the EC has used these specific properties of generic medicines to define them as the

[20] Cf. definition of generic medicinal products in the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, Art. 10, para.2. (b), http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2001L0083:20070126:en:PDF, last accessed July 2011.

[21] Cf. European Generic medicines Association (EGA) website, Paper on "Generic medicines and strict observance of bioequivalence", 2011, available at http://www.egagenerics.com/gen-basics.htm.

closest competitor to the comparative originator product[22].

However, the market investigation may suggest that the demand for generics and originators differs even if the bioequivalence is proven, due to economic factors, such as price differences between them.

Role of economic factors such as pricing and reimbursement schemes as criteria Price differences may be a signal of two different market segments. In the non-pharmaceutical merger decision IV/M062 Eridania/ISI (1992) on the granulated sugar market, the EC pointed out in its analysis of the relevant market that price discrimination may be a sign of the presence of two different product markets. In this specific case, there were two segments, the industrial and food shops, and distribution chains. Both segments correspond to different packaging and different prices. While that could be considered as a sign of a different demand, the EC noted the possibility for the client to make an arbitrage. Indeed no barrier of brand or product differentiation existed between the two segments, so that if the price in one market segment was increasing, clients could buy the other packaging and repackage. Thus, the EC concluded on the existence of one unique relevant market for granulated sugar (Navarro et al., 2005, p. 110-114).

In pharmaceutical markets, the EC has not yet used price differences as a unique signal to define a relevant product market. Demand-side substitution is at first based on medical substitution, such as the bioequivalence between generics and originators. Economic factors, such as price and reimbursement are complementary criteria in an investigation. Thus, in the case COMP/M.5253 Sanofi-Aventis/Zentiva (recital 84 to 102), the EC investigated the activities of the merging firms in the ATC 3 category B1C which is comprised of platelet aggregation inhibitors. They are used in the prevention of thrombotic cerebrovascular or cardiovascular diseases as they prevent the formation of blood clots by preventing platelets, which are a type of blood cell, from aggregating. Since 2000, the ATC 3 category is divided into six ATC 4 categories. Plavix® by Sanofi-Aventis, belongs to the ATC 4 category B1C2 (adenosine diphosphate receptor antagonists) while Asa® by Zentiva, belongs to the category B1C1 (Cyclo-oxygenase inhibitors), containing mainly low dosage acetylsalicylic acid. Asa® is considered as a first-line product for primary prevention and treatment in acute strokes while Plavix® is generally used as a second-line product as an alternative in case of intolerance by the patient to Asa®.

In its reasoning to define the scope of the relevant market, the EC highlighted, besides the different modes of action, and chemical and pharmacological properties, the difference between both products in terms of use. Hence, the fact that Asa® was generised and widely used while Plavix® was new and with a very specific indication was an important implication. The economic difference in terms of price and reimbursement between both products reinforced the EC's view that substitution between both products

[22]Cf. M. 5999, recitals 25-26

was limited and that they did not belong in the same product market. The EC left the market open but concluded that the ATC 3 level was not considered as the right category to define the relevant market.

In the case of pharmaceuticals, the off-patent originator differentiates from the generic product, as it has built a brand recognition during the period while it was patented and hence the only product on the market. However, the EC considers that these differences are not extensive enough to define two separate markets [23]. Marketing expenses are a way to sharpen price competition as "indeed, generic versions of originator medicines are specifically designed to compete with these medicines and normally represent the closest substitute to them" (M.5253 Sanofi-Aventis/Zentiva, rec. 25-26). This statement from the EC is reaffirmed by legislation in most of the EU member states which implemented mandatory generic prescribing and generic substitution. Substitutability patterns between originators and generics, and measures promoting substitution such as rebate contracts, internal or external reference-pricing aim to increase the elasticity of demand of patients and are an indicator for competition authorities that originators and generics belong to the same relevant market. Substitution based on the API, which is promoted by institutional measures, aims to decrease the distortions created by brand loyalty and brand recognition.

Special cases: Defamation practices, parallel trade, "generic-only" markets and off-label use

a. Defamation practices to undermine the bioequivalence of generics The inclusion of the generics in the same product market as the originators becomes questionable if the bioequivalence of generics is undermined.

The Autorité de la Concurrence ("hereinafter ADC") in France was referred to in several defamation cases of generics by originator firms trying to undermine the bioequivalence of the generic versions of their product[24]. In these defamation cases, originators sent to pharmacists and general practitioners through various channels distorted information alleging that the generic versions of their originator product were not bioequivalent in order to create a doubt regarding their substitutability[25].

This was the case in the decision 10-D-16 which concerned the active substance clopidogrel[26]. In this case, the firm Sanofi-Aventis was claimed to have abused its dominant position with its product Plavix® and its authorised generic Clopidogrel Winthrop®, by defaming the generic product manufactured by

[23] Cf. for example case COMP/M. 5865 recital 25.

[24] Cf. Decision n° 07-MC-06 of 11 December 2007 regarding the marketing of Subutex ® generic medications, decision n° 09-D-28 of 31 July 2009 regarding the marketing of Durogesic ® generic medications and decision n° 10-D-16 of 17 May 2010 regarding Marketing of Plavix® generic medications, http://www.autoritedelaconcurrence.fr, last accessed September 2013.

[25] Cf. Decision n° 10-D-16 of the 17 May 2010 regarding Marketing of Plavix generic medications http://www.autoritedelaconcurrence.fr/pdf/avis/10d16.pdf, last accessed September 2013.

[26] Cf. Décision n° 10-D-16 du 17 mai 2010 relative à des pratiques mises en oeuvre par la société Sanofi-Aventis France, available at http://www.autoritedelaconcurrence.fr/pdf/avis/10d16.pdf, last accessed September 2013.

Teva Santé, Clopidogrel HCS®. In order to respect the patent and the supplementary certificate of protection, they differ from the originator Plavix® and its authorised licensed generics in two aspects. First, the clopidogrel salt differs from the one contained in the original Plavix®. Secondly, the indication for acute coronary syndrome (ACS) in association with aspirin is absent in the generic versions as this indication is specifically patent-protected until 17 February 2017.

In all its decisions concerning defamation cases, the ADC adopted a coherent approach as it stated that the marketing authorisation delivered by the competent French or European healthcare authority, Agence Française de Sécurité Sanitaire des Produits de santé (hereinafter AFSSAPS) at a national level at this time, or the EMA at a European level, and then the inscription of the pharmaceutical product in the list of generics both testified to the bioequivalence and the efficacy of the generic with the originator[27]. Thus, by underlining the bioequivalence between generic versions and originator products, the ADC concluded that practices by originator companies were defamatory. It aimed in a more or less implicit manner, to stress the differences between originators and generic products and induced a lack of confidence by healthcare professionals to prescribe or deliver these generic products. In its recent decision 12-D-11 of 14 May 2013[28], the ADC fined Sanofi-Aventis a total of €40.6 million for implementing such a defamation strategy.

The case of the substitutability between Plavix® and its generics was also questioned in Germany. As in the case in France, Sanofi-Aventis argued that generic versions of Plavix® were made of another salt and only partially covered the indications of the originator product. As a result, only a partial substitution existed, in particular for patients suffering from heart failure, but not from acute coronary syndrome[29]. According to the associations of prescribing physicians ("Bundesärztekammer") and health insurance funds ("GKV-Spitzenverband"), the different salt form of clopidogrel which the generic versions contained does not have any impact on the efficacy, the bioequivalence, and the metabolisation of the medicines, but allows patients to be treated with a less costly alternative having the same API[30].

Since the summer of 2009, generic products can also be prescribed for the additional indication in association with aspirin. Generic versions of clopidogrel quickly attained large market shares, also before the unlimited substitution in association with aspirin. While in the third quarter of 2008, only 9 % of patients were treated with a generic version of clopidogrel, prescriptions of generic versions of clopidogrel

[27] Cf. Décision n° 09-D-28 du 31 juillet 2009 relative à des pratiques de Janssen-Cilag France dans le secteur pharmaceutique, par. 127, p. 22, last accessed September 2013.

[28] Cf. Décision n° 13-D-11 du 14 mai 2013 relative à des pratiques mises en œuvre dans le secteur pharmaceutique, available at http://www.autoritedelaconcurrence.fr/pdf/avis/13d11.pdf, last accessed September 2013.

[29] Gräfe K., "Clopidogrel: Substituieren - Ja oder Nein?", Pharmazeutische Zeitung online, Ausgabe 33/2008, available at http://www.pharmazeutische-zeitung.de/?id=28841, last accessed August 2013.

[30] Cf. Kassenärztliche Vereinigung Berlin: Information im Rahmen der Arzneimittelvereinbarung 2009 auf der Grundlage des § 73 Abs. 8 SGB V - Hinweise zur Verordnung von Clopidogrel, http://www.kvberlin.de/20praxis/50verordnung/10arzneimittel/clopidogrel_090609.pdf, last accessed February 2011.

in the third quarter of 2009 represented around 43% of the sales of clopidogrel products (INSIGHT Health, 2010). Due to the implementation of the rebate contracts based on the API, the competition between generics is sharper and the market shares of generics are increasing.

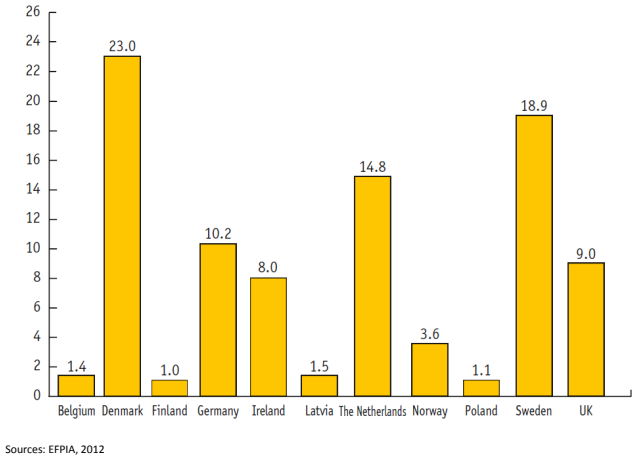
b. Competition between patented products: The case of parallel trade products Within the competition status (patent-protected or off-patent), different competition patterns can be observed. For patented products, competition takes place mainly within therapeutic grounds, meaning based on the different APIs among the different alternatives which are imperfect substitutes.

However, the existence of the parallel trade of products with the same API among the EU member states enables perfect patent-protected substitutes to compete with each other. Parallel trade consists of the purchase by parallel trade distributors of pharmaceuticals in low-priced countries in order to export in high-priced countries.

Parallel trade distributors use the possibility of making a "regulation-derived arbitrage" to bypass the price differences of medicines between the countries (Kanavos et al., 2005, p.755).

Definition and rationale of parallel trade The pricing of pharmaceuticals involves a trade-off between rewarding innovation by recovering high R&D costs, and the considerable leverage of governments to contain escalating pharmaceutical expenses. Moreover, the income per capita and preferences differ across countries, even within the EU, so that the price setting of pharmaceuticals is adjusted to the demand price-elasticity of each country leading to a price-discrimination across countries.

Figure 2.1: Share of parallel imports in pharmacy market sales (in %, 2012)



Benefiting from the EU-wide principle of the free movement of goods, parallel trade mainly affects the most innovative and high-priced pharmaceuticals as the price differences for these products is the highest (see figure 2.1). This phenomenon is also called "cherry-picking" (Barfield et al. 1999, p.195). After the patent expiration of an originator, generic competition leads to decreasing prices and parallel trading stops.

Indeed, the parallel trade of medicines is the only way for in-patent medicines to induce price competition in the market. In an unregulated market, the arbitrage would give rise to a Bertrand-price competition across countries and a downward price equalisation like in a generic market without price regulation.

Parallel trade products and the relevant product market In those member states such as Germany where the price of medicines is pretty high compared to the other EU member states, the import of parallel trade products represents an interesting healthcare containment policy instrument. Incentives for pharmacists to deliver imported medicinal products are provided for as they can benefit from the savings made between the price of the product coming from the legal chain and the imported product.

This legal obligation to deliver the cheapest parallel or re-imported product, or to create an obligation to deliver a certain percentage of parallel or re-imported medicinal products is complementary to the promotion of generic substitution.

Parallel trade creates, therefore, a competition between the products coming from the legal chain and those from parallel trade. These two channels have to be taken into account when defining the relevant market as it creates price competition especially in the segment of patented innovative medicinal products where no competition in price is deemed to exist.

Legal analysis of parallel trade Parallel trade decisions on a breach of article 102 TFEU by the EC and the European Court of Justice (hereinafter "ECJ", now the Court of Justice of the European Union, "CJEU") of a pharmaceutical manufacturer trying to restrict parallel trading are numerous. For example, in the SYFAIT/GlaxoSmithKline case in 2004[31], GlaxoSmithKline (hereinafter "GSK") stopped supplying its wholesalers in Greece because the wholesalers exported a substantial proportion of the products to higher-priced member states which led, according to GSK, to shortages in the Greek market. For this reason, it decided to directly supply pharmacies and hospitals. However, this was considered by the wholesalers as a breach of article 102 TFEU. The question of whether a dominant pharmaceutical firm can entirely refuse to supply a wholesaler's orders as a response to limit parallel trade was referred

[31] Cf. C-53/03 Syfait and others v Glaxosmithkline, 28 October 2004, available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:62003J0053:EN:HTML.

to the ECJ by the Greek Competition Commission.

The ECJ found that it lacked jurisdiction and declined to rule. In the joined cases C-468/06 to C-478/06 (hereinafter collectively Syfait II), the ECJ concluded that the Community rules on competition cannot be interpreted in such a way that GSK would not be able to fill orders to defend its commercial interests, unless these orders were considered as "out of the ordinary" (United Brands C-27/76). This conclusion means that a firm holding a dominant position which, in order to stop parallel exports, refuses to meet the ordinary orders of some wholesalers, is abusing its dominant position. It is the mission of the national courts to decide whether the orders are considered as "ordinary" depending on their size and the previous business relations between the firm involved and the wholesalers.

In parallel trade cases, the definition of the relevant market is a key concern and covers certain specifics. Indeed, parallel trade depends on the arbitrage margins between the products in the various EU member states. The EFPIA notes that traders and wholesalers involved in parallel trading are only concerned by price differentials across countries (EFPIA, 2004, pp.31-32). Quoting Jenny: "if two drugs have the same potential profit margin, it is possible that they can be considered to be substitutes by parallel exporters" (Jenny, 2002).

Thus, Siebert and Priest (2007) propose as a criterion to define the relevant market, not the therapeutic demand from prescribing physicians or patients, but the profitable price difference between member states (Siebert and Priest, 2007, p. 150).

c. Competition on off-patent markets and the "generic-only" markets While generic products have an obligation to demonstrate bioequivalence with the off-patent originator and are therefore considered as their closest substitutes, Morse (2003) explains that, in some occasions, the US courts might define "generic-only" markets[32].

Price differences and the definition of generic-only markets Morse (2003) suggests that the competition degree and the existing price differentials on the generics markets are a decisive variable to define "generic-only" markets or not. When the price differential between the originator product and its generic versions is important, consumers are going to consider low-priced products and higher priced products as not interchangeable. Such a price differential might especially happen because originator products rely on the brand loyalty and the brand recognition of loyal consumers to continue charging higher prices than their generic versions.

[32]Cf. FTC v. Biovail Corp. & Elan Corp., FTC Docket No. C-4057 of 15 August 2002, Respondents´ market power, par. 6, available at http://www3.ftc.gov/os/2002/08/biovalcmp.pdf. Generic-only markets were also defined in the non-merger case, FTC v. Mylan Laboratories, para. 17, http://www.ftc.gov/os/1998/12/mylancmp.htm, last accessed February 2011.

Morse explains that in markets with few generic manufacturers, the price differential is usually lower so that consumers would consider products as interchangeable. The degree of generic competition in the market puts pressure on the molecule level, meaning at ATC levels 4 and 5, and not on the therapeutic level corresponding to ATC level 3 which results in a decrease of the scope of the relevant product market. However, Morse (2003, pp. 15-16) also notes that in the US, the courts do not consider price differences as "determinative" to define separate relevant product markets. Instead, it is the "responsiveness to price changes", meaning the result of the SSNIP test, which is of importance in defining the scope of the relevant product market.

Analysis of the EC at the ATC level 4 Without ever mentioning the expression of "generic-only" markets, the EC in the merger case Teva-Barr[33] departed from its analysis at ATC level 3 and focused on the ATC level 4. It justified its choice by mentioning that the merger was taking place between generic manufacturers and that, for the products concerned, the competition was taking place at the molecule level, which was consequently playing an important role.

This specific configuration, combined with the fact that the EC used information at the molecule level for its Sector Inquiry (EC, 2009), these are signals that generic-only markets may be suitable to define the scope of the relevant product market. This focus on the molecular level tends then to narrow the size of the relevant market at this level, meaning the ATC level 4 or 5. This focus is enhanced by the specific patterns of competition on off-patent markets where originator products try to differentiate as much as possible from their generic versions by means of advertising and not on therapeutic grounds.

These features cannot be classified in an objective way. By definition, generic medicines are comparable in quality to their comparator product but they do not have the recognition of the off-patent originator, or the brand loyalty that the off-patent originator built while it had the market to itself.

As for the focus on the molecule level to define the relevant product market, the EFPIA (EFPIA, 2004, p. 25) reacted by stating that defining the relevant market at the molecule level was the result of an erroneous application of the relevant product market principles. For the EFPIA, substitution patterns should be investigated at the prescribing stage, meaning when the physician chooses the product to prescribe and not at the level of the pharmacist once the prescription has been written. Defining the market on the molecule level implies that firms with low market share in a therapeutic class would be likely to be found to have market power. Hence, it concludes that "market power implies a significant, lasting power over a meaningful category of products, not merely the temporary "power" that every seller has over the sale of its own product." (EFPIA, 2004, p.25)

[33]Cf. Case No COMP/M.5295 -Teva / Barr.

While a trend to narrow the scope of the relevant product market at ATC levels 4 and 5 is perceptible, the starting-point of the EC's analysis remains the therapeutic level (ATC level 3) to define the basis of the demand substitution patterns.

d. Off-label use The term off-label use refers to the prescribing of a pharmaceutical for an unapproved use (unapproved indication, age group, dosage or form of administration)[34].

The off-label use can be employed, for example, by pharmaceutical firms to avoid the high costs of clinical trials needed to get marketing approval in the case of rare indications. Priest and Siebert (2007, p. 151) offer the example of the medicine Avastin. Avastin is made of the active substance bevacizumab which blocks the growth of new blood vessels and is used to treat i.a. colorectal, lung, and kidney cancer. Besides these indications, it is also prescribed off-label to treat macular degeneration, as in the proliferation of blood vessels in the retina.

Off-label use is mainly observed for an indication or a dose other than the approved one, a patient in an inappropriate age, for a different route of administration, an inadvisible co-prescription or a different stage of the disease. Off-label use is important in the treatment of rare diseases, as the orphan designation is still scarce.

Off-label use may or not be reimbursed depending upon national legislation. In France for example, the law on the strengthening of the safety of medicines and health products (Loi relative au renforcement de la sécurité sanitaire du médicament et des produits de santé) which was adopted by the National Assembly on 19 December 2011[35] provides in article 18 that off-label use prescription is authorised when no alternative exists with a marketing authorisation or a temporary authorization usage (so-called "Autorisation Temporaire d'Utilisation", hereinafter ATU). However, a recommendation of temporary usage (so-called "Recommendation Temporaire d'Utilisation", hereinafter RTU) must have been granted by the health regulatory authority (Agence nationale de sécurité du médicament et des produits de santé, hereinafter ANSM, ex-AFSSAPS) for the indications or the conditions of clinical use for a maximum of three years, or if the prescriber judges it indispensable for the patient. Article 16 of the law provides that when no appropriate alternative is available, medicinal products for the treatment of a chronic or an orphan disease subject to a RTU are reimbursed by way of derogation for a limited time.

For relevant market consideration concerns in the case of off-label use for a medicine, Priest and Siebert (2007) consider that demand substitutability is better taken into account through the prescription

[34]Cf. Tolle A., Meyer-Sabellek W., Off-Label-Use Möglichkeiten und Grenzen aus der Sicht der pharmazeutischen Entwicklung, Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2003, n°46, pp. 504–507, available at http://www.springerlink.com/content/btv97qhnpprjvm0j/fulltext.pdf, last accessed December 2011.

[35]Cf. loi relative au renforcement de la sécurité sanitaire du médicament et des produits de santé, available at http://www.assemblee-nationale.fr/13/ta/ta0805.asp, last accessed August 2012.

practice of physicians thus the needs of the prescribing physician rather than the sole indications provided by the market authorisation. Prescription practice differs depending on the national regulatory and reimbursement systems. When off-label use is reimbursed, physicians will be more likely to prescribe off-label. In this respect, the EC has not made any decision.

2.1.3.2 Distinction by prescription status: Rx/OTC

Access to pharmaceuticals is regulated through physicians and pharmacists contrary to other consumption goods. Pharmaceuticals are, as a general rule, prescribed by a physician, but some can also be sold over-the-counter (hereinafter OTC) depending on the national legislation.

Rationale for OTC launch and OTC switch Over the last decade, the core business of pharmaceutical firms has expanded towards new medicines. The switch of a medicinal product from an on-prescription only status (so-called in the specialised literature "Rx") to an OTC designation is visible for indications such as respiratory, digestive diseases and pain in cases where patients are fully involved in the choice of their treatment and are willing to bear the costs. This switch is also a consequence of the reimbursement policy of health insurance funds, which are increasingly relying on HTA based on medico-economic studies that are raising barriers to entry for new pharmaceuticals to prove their medical added value. Switching to the OTC designation allows firms to create line extensions to transfer the brand recognition and brand loyalty they have been built on via the prescription market to the OTC segment and hence compensate the non-reimbursed status of OTC. OTC switching is therefore the result of an optimisation problem by firms relying on the trends towards self-medication and the empowerment of patients becoming consumers or producers for their own health as well as the increasing competition with other channel modes such as drugstores, discounters and mail-order shops.

These ongoing multifaceted strategies of launching OTC products, allow firms to price discriminate while charging higher prices and maintaining significant market shares, in particular when a patent is about to expire and a threat represented by generic competition exists in order to gain a first-mover advantage. By switching to OTC, a firm is balancing the costs of an application with the probability of approval by the administrative institutions and the probability of generic entry. For example, in May 2009, the patent for pantoprazole (a PPI used in the treatment of dyspepsia and peptic ulcer disease) expired in Germany and other EU member states. Since mid-July 2009, OTC versions of pantoprazole have been available in the German market (Insight Health, Markttrends, August 2009). Nycomed, the firm who held the patent, applied towards the EMA in anticipation of the patent expiry to get a market authorisation for an OTC version of pantoprazole.

A similar outcome happened the same year with omeprazole, which is also a PPI and which was withdrawn from compulsory prescription in Germany, in August 2009. In the indication for heartburn, the maximal dose per day is 20mg for 14 days. To facilitate the introduction of its OTC omeprazole "Omeprazole dura", the generic manufacturer Mylan chose eight different forms of packaging, containing seven or fourteen hard capsules and launched an advertising campaign with flyers and CD-ROMS for consumers. The OTC products distinguished themselves through their good quality to price ratio.

Differences between OTC and on-prescription drugs The characteristics of these newly launched OTC products differ from medicines prescription, by their medical indications, side effects, legal framework, as well as their distribution and marketing systems.

Consequently, OTC advertising can be directly targeted to the patient who buys the product and bears the costs, while advertising for Rx is only allowed towards prescribing doctors through sales representatives, for example, or medical literature and congresses[36]. Hence, the price elasticity of demand for OTC products is expected to be higher than for on-prescription drugs. Consumers´expectations towards an OTC product differ from that of a prescription product. Patterns for OTC, in terms of consumption and distribution, are closer to that of the consumption goods than to on-prescription drugs.

For products sold on prescription, the focus is set on no-name generics which compete through prices, guided by the Health Insurance Funds, or expensive new products with a proven medical added value. However, in the OTC market, the brand is an essential part of the patient's decision to purchase as it goes along together with advice, quality, support and higher prices. Consequently, an OTC has a key role in the pharmacy, as well as the packaging of the product, and the launching of advertising campaigns.

The reimbursement rule only partially corresponds to the distinction on-prescription/OTC. Indeed medicines which can be purchased both on-prescription and OTC can, as a general rule, be reimbursed in EU member states. The need of patients to buy an OTC is not only a functional one as in the case mostly for prescribed medicines, but also an emotional one, based on different criteria.

Defining the relevant product markets for OTC In numerous merger cases, the EC defined separate relevant product markets for both types of medicines because of their differences in terms of medical indications (including possible side-effects), legal framework, marketing, distribution and rules on reimbursement. However, it might happen that Rx and OTC products only differ by their package size, dosage or galenic form[37]. Hence, it concluded that an assessment was needed on a case-by-case basis in order to make a market distinction between OTC and Rx products. However, the EC notes that, for diseases with-

[36]The marketing of on-prescription medicines targeting patients is forbidden in the EU.
[37]Cf. COMP/M.5253 Sanofi- Aventis/Zentiva, rec. 21-23).

out gravity, OTC and on-prescription markets may be more closely related and might belong to the same relevant product market. Buying an OTC product allows the patient to avoid a visit to their prescribing physician.

Galenic form as a determinant of demand-substitution OTC medicinal products differ from on-prescription products by their package size, dosage, and galenic form. In the case COMP/M.5865 Teva-Ratiopharm, the EC refers to the galenic form as a combination of features including the "dosage, pharmaceutical form and route of administration" which may restrict the substitutability of two medicines to some extent.

OTC often have a lower dosage than on prescription drugs. The galenic form of a medicinal product is a key characteristic as drugs do not only differ by their active substance. Therefore, the EC is of the opinion that in some cases, such as paediatrics "different routes of administration of a medicine are, in general, designed to serve the needs of different patient groups and are therefore not interchangeable" [38].

For example, the patch technology market for narcotics (ATC level 3 N2A) which was investigated by the EC in the merger case COMP/M.5865 Teva-Ratiopharm, differs from oral formulation as it is slow-release and presents different effects in terms of efficiency and immediacy than other formulations.

Hence, the galenic form may be the sign of a different demand from the patients which is not always reflected in the ATC classification. Demand-substitutability patterns may be reinforced by supply-side substitution patterns. In the case of M.5865 Teva-Ratiopharm, the EC stressed from its market investigation that the development of a new galenic form was around two to three years so that, for supply-side considerations, both galenic forms (oral formulation and patches) do not belong to the same relevant market[39]. Thus, supply-side substitutability, related to know-how and manufacturing facilities, is not immediate, and therefore should not be taken into account in the analysis.

When the products under consideration are only OTC, the market definition may differ from the relevant market defined with the same products on-prescription. In the merger case COMP/M.3544 BayerHealthcare/Roche OTC Business[40], the EC investigates the product market for H2 Antagonists and Antacids. It noted that H2 antagonists (ATC level 4 A2A1) are considered as stronger than antacids (ATC level 4 A2B1). However, due to the lower dosage authorised for both active ingredients, these OTC products can be considered as belonging to the same product market, because they both treat the same level of disease gravity. As a consequence, the OTC status blurs the frontiers within the ATC categories.

[38] Cf. COMP/M.5865 Teva-Ratiopharm, rec. 17
[39] Cf. COMP/M.5865 Teva-Ratiopharm, rec. 18
[40] Cf. COMP/M.3544 BayerHealthcare/Roche OTC Business, rec. 19-20.

2.1.3.3 Distinction by means of distribution: hospital markets/pharmacy markets

Medicinal products can be sold in pharmacies or through hospitals which represent two different market segments. Drugs for hospital use often differ from medicines sold in pharmacies regarding their galenic form.

Hospital medicinal products and galenic forms In the case COMP/M.5253[41] Sanofi-Aventis/Zentiva, the EC investigated the fluoro-quinolones (J1G) market, which are synthetic broad-spectrum antibiotics. The category J1G contains old and new molecules, but the market is defined according to the galenic form of a drug.

The EC explains that fluoro-quinolones exist in oral and injectable form. The injectable form, which is mostly used in hospitals as perfusion, is the most convenient method of administration for bedridden patients[42]. In the case M.5253, the EC investigated whether injectable high molecular weight (unfractionated) heparin (hereafter "UFH") and the newer generation of injectable low molecular weight (fractionated) heparins (hereafter "LMWH") which are classified in the same ATC level 3 (B1B) both belong to the same relevant market. Based on market investigation, both products have largely common indications. However, this investigation confirmed that UFH could only be used for inpatient care under constant monitoring by a physician contrary to LMWs which can be used by outpatients without constant monitoring. By stressing that the hospital segment represents more than 80% of the total market for B1B, the EC concluded that it was to be considered as a separate segment of the heparin market[43].

Differences in pricing and reimbursement schemes Besides the issue of galenic form, which may be specific for inpatient care, pricing and reimbursement patterns often differ significantly between pharmaceuticals sold in pharmacies and those delivered in a hospital.

Siebert et al. (2007, p. 151) therefore explain that in Germany, the expected price and margin for pharmaceuticals sold in pharmacies is regulated in paragraph 78 of the law for medicinal products ("Arzneimittelgesetz", hereinafter AMG)[44] while hospital medicinal products are excluded from this legislation[45]. Siebert et al. conclude that this specific legislation for hospital use of medicinal products is the sign of a segmentation in the market between these two different means of distribution.

In France, while as a general rule the pricing of pharmaceuticals is set by decree after an assessment

[41] Cf. COMP/M.5253, rec. 121 and ff..
[42] Cf. COMP/M.5253 Sanofi-Aventis/Zentiva, rec. 121-126.
[43] Cf. COMP/M.525, rec. 77-81
[44] Cf. http://www.recht-in.de/paragraph/preise_paragraph_78_amg_arzneimittelgesetz_111618.html, last accessed July 2012.
[45] Cf. par. 1, subpar. 3 of the law on the pricing of medicinal products (Arzneimittelpreisverordnung, hereinafter AMPreisV).

of its clinical benefit, the price of hospital products is set freely between the hospital and pharmaceutical companies. For most hospital pharmaceuticals[46], funding for hospitals and reimbursement occur through an activity-based payment (so-called "Tarification à l'Activité", hereinafter T2A) by means of diagnosis related groups, so-called "Groupes homogènes de séjour", hereinafter GHS (Natz et al. 2012a).

For these reasons, the substitutability between products sold in pharmacies and delivered at hospitals is limited, and hospital and pharmacy markets do not constitute the same relevant product market.

The EC also stresses in its market investigations, that competitive tenderings based on the molecule level often take place in the different EU member states for the supply of hospitals pharmaceuticals. For serious diseases, hospitals would not switch to another molecule even in the case of a price increase [47]. Demand substitution patterns are based on thus the molecule level and result in narrowing the scope of the relevant market.

"Source effect" in a hospital After a visit to the hospital, patients often have to continue their treatment with the same pharmaceutical product or the same active ingredient, with possibly another galenic form which is more convenient for outpatient use. This effect is commonly called the "source" or the "follow-on effect" and was investigated in several antitrust cases.

The term "source effects" refers to the treatment of a patient by using a medicine in hospital which is continued after the hospital stay due to the presence of high switching costs. The presence of these "source effects" would have a considerable impact on the relevant market definition as it would imply that both market segments (pharmacy and hospitals products) belong to the same relevant product market.

In the Napp case[48], the Office of Fair Trading (hereinafter "OFT") found Napp's pricing policies for a sustained release morphine product used as a painkiller for cancer, to be both predatory on the hospital segment and excessive on the community market. Napp held a patent on its drug which expired in 1992 and started to supply hospitals through predatory and exclusionary practices (anti-competitive targeted discounts) and as a consequence was charging excessive prices within the pharmacy markets.

Napp's pricing policy, which was aimed at raising barriers to entry in the hospital segment, was found to be the principal means to enter the market for this specific product. Hospital and pharmacy sectors were considered to be distinct. However, links exist due to referrals and the effects of reputation so that the drug's availability in the hospital sector impacts positively on the position of the product in pharmacy market. Napp was found to have a dominant position in both markets.

[46] Three categories of hospital pharmaceuticals, hospital ambulatory medicinal products, innovative medicines, and pharmaceuticals having been granted an Authorisation of Temporary Usage ("Autorisation Temporaire d´Utilisation", ATU) have a special price and reimbursement framework.

[47] Cf. COMP/M.5295, rec. 14

[48] Cf. case No. 1001/1/1/01, Napp Pharmaceutical Holdings Limited And Subsidiaries and Director General Of Fair Trading, January 2002.

However, these alleged links and "follow-on" effects on the community market are considered as neither predictable nor systematic. In its decision No 10-D-02 of the 14 January 2010 on the Sanofi-Aventis' free-of-charge policy on its low molecular weight heparin drug sold to hospitals in France, the ADC separated pharmacy markets from hospitals markets as the alleged practices were only involved hospital markets. It concluded, however, on the "source effects" between hospital and community markets. Pharmaceutical companies have strong incentives to be present in the hospital segment at the initial prescription stage in hospitals and hence supply at a very low price to these markets in order to be later present in pharmacy markets at a much higher price. The ATC stressed that for these types of pharmaceuticals in particular high switching costs exist for the physician.

The definition of the relevant product market for pharmaceuticals is hence not straightforward and requires taking into account the specifics of the sector. While the ATC level 3 is appropriate to start the analysis, a case-by-case study is needed to refine it.

2.2 Econometric analysis of the EC approach of market definition in merger cases

Once the purpose and the method of the empirical study have been described (2.2.1), the variables used in the econometric analysis (2.2.2), as well as the models are presented (2.2.3). Finally, some conclusions and policy implications are drawn for the whole sample 1989-2011, and in particular for the sub sample 2004-2011 (2.2.4).

2.2.1 Description of the empirical study on market definition in merger cases

The aim of the empirical study is at first analysed (2.2.1.1) before describing the method which will be used as the related literature (2.2.1.2).

2.2.1.1 Aim of the empirical study

As stressed in the previous sections, the substitutability of medicinal products is the key decision criterion to define the relevant market so that

> "the relevant inquiry is not whether products compete against each other in some broad sense but whether products are sufficiently substitutable that they could constrain each other´s price" (Morse, 2003, p. 664).

No economic study has yet analysed EC's decisions on the relevant market in merger cases in an econometric way, in order to achieve a precise examination of the demand and supply-side factors that the EC takes into account in its analysis, and which leads to the choice of a broad or a narrow market definition.

From the conclusions of the EC's decisions, a noticeable trend exists to define narrower markets over time which is of interest to study. The EC, while deciding on the scope of the relevant market in antitrust and merger decisions, explains the criteria behind its decisions on the scope of the analysis. No econometric study analysed which criteria were the most significant to define the scope of the relevant product market. It is important for firms to have an overview of the factors which explain the EC's decisions, hence the factors which, for the EC, represent the demand-side substitution patterns and also eventually supply-side factors and future markets in order to foresee them.

Importance of the scope of the relevant market The scope of the relevant product market is a key issue for firms in dominance and merger investigations. It is not rare for the EC to disagree with the market definition proposed by the parties involved in the merger or the alleged dominant position. With

regard to mergers, a narrow market definition decreases the possibility of overlapping products, while in dominance investigations, it increases the probability for a firm to be found dominant. However, article 102 of the TFEU only applies in cases where the firm concerned has a dominant position in the relevant product market.

For example, in the AstraZeneca case in 2005[49], the definition of the relevant market concluded that the firm AstraZeneca held dominance within the PPIs market. Indeed, the EC found that AstraZeneca's product, Losec, did not belong to the relevant market of antihistamines (H2 blockers). While both treatments are in the same ATC level 3 which is the traditional starting-point for an analysis, their mode of action differs significantly. In the EC's view, this difference in their mode of action has an impact on the demand substitutions for both products. Hence, it defined the relevant product market at the ATC level 4. AstraZeneca claimed that the EC wrongly assessed the relevant market for stomach ulcers and that it was not dominant within the market.

Trend to define narrower relevant markets The EC's trend of defining narrow markets based on the active substance, so-called "molecule markets" which would correspond to ATC level 4 or even narrower at the ATC level 5, is particularly noticeable in merger investigations. In this narrow analysis of the EC, any product protected by a patent may be found retrospectively dominant during its patent protection.

The EC's analysis in the AstraZeneca case was later confirmed by the General Court of the EU which based its decision on the mode of action, the actual use of both products, and the physician's prescribing patterns. While PPIs treat serious forms of stomach ulcers and other acid-related disorders, H2 antagonists are used to treat mild conditions.

> "While H2 blockers only block one of the stimulants of the proton pump, namely the histamine receptors in the parietal cells, PPIs operate on the proton pump itself. In the contested decision, the Commission thus found that H2 blockers only operated indirectly on the proton pump, whereas PPIs had the ability to operate directly on the proton pump. Next, it should be noted that it is common ground that the therapeutic strength of PPIs is significantly greater than that of H2 blockers. The parties also agree that sales of PPIs increased significantly and that sales of H2 blockers fell significantly."[50]

[49] Cf. AstraZeneca AB and AstraZeneca plc v European Commission, case T–321/05, European Union General Court (Sixth Chamber, extended composition), Judgment of 1 July 2010, available at http://curia.europa.eu/juris/celex.jsf?celex=62005TJ0321&lang1=en&type=NOT&ancre=, last accessed Juny 2011.

[50] See AstraZeneca AB and AstraZeneca plc v European Commission, case T–321/05, European Union General Court (Sixth Chamber, extended composition), Judgment of 1 July 2010, par. 62-63

2.2.1.2 Approach of the empirical study and related literature

How the study is going to identify the important substitution criteria In the following, an econometric analysis of the EC merger decisions will be performed and will focus on the review of substitution patterns in merger cases, as market definitions in merger cases are more numerous than in dominance investigations.

The aim of this empirical study is to examine in an econometric approach the EC's merger decisions on pharmaceutical markets between 1989 and 2011 as well as the criteria it gave to explain the scope of the relevant market and investigate whether the EC applied these criteria consistently.

The knowledge of these factors and any potential trends, with regards to the scope of the market definition, can be helpful for firms in order to foresee the EC's definition of the relevant product market and to give them more certainty while proposing a market definition which would be more likely to be accepted. The aim is, for each relevant market investigated, to identify the substitution factors which led the EC to define the scope of the relevant market broadly or narrowly.

According to the economic theory of the relevant product market and the Commission notice on the relevant market, demand-side factors are to be primarily taken into consideration. In addition, other variables irrelevant from a demand-substitution point of view, such as political variables, may potentially influence the decision. This may be the case if the EC has allowed for political pressures in its market definition. Moreover, over time the factors may change, for example due to the new merger regulations which came into force in 2004 and replaced the previsous one.

How this study is related to other works Various economic papers reviewed, by means of econometric instruments, the EC's decision with regards to merger cases and dominance investigations. Three articles in particular might be compared to this empirical study.

Firstly, Schinkel et al. (2006) who focused on antitrust decisions and provided from 1964 to 2002 a statistical analysis of the probability of infringement and appeal in a binary probit model. By taking into account variables such as the report route, duration, length of the decision, economic rationale, imposed fines, number of parties involved, sector classification and Commissioner in charge, they studied the determinants which impacted the probability of infringement and of appeal to the ECJ. They found that notified cases in which abuse of dominance played a role was more likely to lead to an infringement, while the main determinant for appeal was the level of the fines imposed.

Secondly, Bergman et al. (2003) who reviewed in their paper the factors influencing the EC's merger decisions. Using a sample of 96 mergers notified to the EC from September 1990 to October 2002 and regressing them via a logit model, they found that the probability of a phase II investigation and of a

prohibition of the merger increases when the parties´ market shares were elevated in the presence of high entry barriers or when post-merger collusion was likely to be easy. They did not find any significant effect of possible "political" variables, hence the EC's decisions were not influenced by political factors.

Finally, Bougette and Turolla (2006) reviewed in their empirical paper 229 merger remedies between 1990 and 2004 via three different multinomial models. They focused on the characteristics of merging firms in order to explain the merger remedies and estimate the relationship between the merger remedy decisions and market structures. They found that remedies are more likely in the presence of high market power and in innovative industries as well as during Competition Commissioner Mario Monti who, more than previous Commissoners, looked for concessions from the merging parties.

Characteristics of the following empirical study To my knowledge, no economic paper has ever specifically analysed the criteria used to define the relevant market on pharmaceutical markets in merger decisions.

All of the above-mentioned studies investigated EC decisions through logit or multinomial models, because information and quantitative data, which are likely to be highly business relevant, are often hidden. In logit models, information is coded in binary outcomes.

The aim of the following empirical study is to find the main criteria the EC takes into account in its analysis and how it determines the scope of the relevant market. The following analysis will follow the same approach as the afore-mentioned works but will focus on merger cases within pharmaceutical markets. Merger cases do not contain any informative figures with the exception of the merging firm's global turn-over. Consequently, in order to perform an econometric analysis, the information contained within the merger decisions will be coded.

2.2.2 Variables and data description

Once the data collection process has been described (2.2.2.1), the dependant and explanatory variables are presented (2.2.2.2). Finally, a description of the statistics is performed and discussed (2.2.2.3).

2.2.2.1 Data collection

Data was collected from the EC's website, Directorate General for Competition, and consists of all of the mergers between 1989 and 2011 notified to the EC with the code C21 in the statistical classification of economic activities in the European Community (in French: Nomenclature statistique des activités économiques dans la Communauté européenne, commonly referred to NACE), which corresponds to the

"Manufacture of basic pharmaceutical products and pharmaceutical preparations"[51].

From 1989 to 2011, 106 merger cases with the NACE code C21 were notified to the EC. All cases were covered by two regulations, the regulations 4064/89/EEC[52] and from 2004 onwards the European Merger Regulation 139/2004/EEC (hereinafter ECMR)[53].

In the ECMR, the fundamental philosophy of the previous regulation is maintained, but important procedural changes were introduced that may have a potential impact on the definition of the relevant market. It specifies the thresholds for a merger to have a Community dimension and the definition of the term "concentration". Just some of the interesting innovations in the ECMR are: the revision of the "best practices" guidelines, the jurisdictional flexibility of the new referral requests (so-called "Form RS"), the official forms for standard merger notifications (so-called "Form CO"), and the change in the substantive test. While the old test was expressed in terms of dominance, the revised substantive test states that:

> "a concentration which would not significantly impede effective competition in the common market or in a substantial part of it, in particular as a result of the creation or strengthening of a dominant position, shall be declared compatible with the common market". (ECMR, 139/2004/EEC, art.2)

The revised substantive test gives the EC more flexibility to justify its decision when a merger is found to significantly impede effective competition and to challenge mergers that do not lead to the creation of a dominant position but are likely to raise prices through non-collusive behaviours.

Data processing Among the 106 mergers cases, no useful information on the relevant product market is available when the merger is withdrawn by the parties, or in the case of a simplified procedure[54]. In addition, among the 106 notified mergers in the given NACE code C21, some mergers did not cover pharmaceuticals but other agricultural products or diagnostics which are not grouped using the ATC classification.

This analysis has chosen to focus on markets which were defined with reference to the ATC classification. After applying the filters mentioned, the sample of market definitions being investigated consists

[51] Data available at http://ec.europa.eu/competition/elojade/isef/index.cfm?clear=1&policy_area_id=2, last accessed November 2011.

[52] Available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31989R4064:EN:HTML, last accessed November 2011.

[53] Available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:024:0001:0022:EN:PDF, last accessed November 2011.

[54] If the concentration satisfies the criteria for a simplified procedure, the EC will issue a short-term for decision. The simplified procedure is used for concentrations that "are normally cleared without having raised any substantive doubts, provided that there were no special circumstances", see Commission Notice on a simplified procedure for treatment of certain concentrations under Council Regulation (EC) No 139/2004, I.1, available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2005:056:0032:0035:EN:PDF, last accessed November 2011.

Table 2.1: Description of the sample

Total sample	217
-Number of market definition investigations where the parties expressed their views	173 75 (43%)
• Number of market investigations where the parties agree with the ATC level 3 being the relevant product market definition level	112 (65%)
• Number of market investigations where the EC agrees with the ATC level proposed by the parties	

of 27 mergers decisions, representing 217 analyses of the relevant market which can be investigated, as shown in table 3 which describes the sample used.

2.2.2.2 Dependent and explanatory variables

Dependent variable The dependent variable is the scope of the relevant market which is decided by the EC at the end of its market investigation in order to assess the competitive effects of the merger.

It is common for the EC not to conclude on the scope of the relevant market, in order to not create a precedent for future merger cases. When the EC, based on consumers and competitors market surveys, concludes that there are "strong indications" regarding the market definition at a certain level, it has been interpreted as a hint regarding the scope of the relevant market and has been included in the data.

The starting point for the EC's analysis is the third level of the ATC classification (meaning the therapeutic intended use of a product) which depends upon the specific substitution patterns, and may depart from it in its conclusions on the relevant market.

In this empirical study, the dependent variable is coded and takes two values (0 or 1) depending on the EC's decision regarding the scope of the relevant market. The value 0 means that the market was broadly defined at the ATC level 3 or even broader. The value 1 means the market was defined at a narrower level, either ATC level 4 or 5 (molecule level). A definition of the relevant market at ATC level 5 did not happen before 2004.

Explanatory variables The explanatory variables employed in the regression consist of variables representing demand-substitution patterns, supply-substitution patterns, political variables, as well as variables which take into account the specifics of each particular market investigated.

Variables taking into account the demand and supply-side substitution patterns Seven variables, all dummies, take into account the different demand-substitution patterns mentioned by the EC when defining the relevant product market:

1. *Intended use and gravity of the disease*: This variable describes the therapeutic intended use of a product and the gravity of the disease it is intended for. It takes the value 1 when the EC judges that the intended use of the product is a suitable criterion for defining the relevant market. This variable also corresponds to the difference between first-line and second-line treatment.

2. *Efficacy of the product*: This variable describes the presence of molecules of different generations in the ATC level 3, meaning new products having a higher efficiency than older products. The variable takes the value 1 when the EC judges that the presence of new generation molecules in the ATC level 3 category have a higher efficacy or new modes of action impacts the demand-substitution patterns.

3. *Active ingredient*: This variable describes the composition of the products in the ATC level 3 category. It takes the value 1 when the products in the ATC level 3 differ by their active ingredient or molecule, which impacts the demand-substitution patterns.

4. *Over-the-counter medicines*: This variable describes the presence, among prescription medicinal products in the ATC level 3, of products sold OTC. It takes the value 1 when the EC found that OTC products are present and impact the demand-substitution patterns.

5. *Galenic form*: This variable describes the presence in the ATC level 3 category of medicines having a different galenic form, meaning the dosage, the pharmaceutical form and the route of administration. It takes the value 1 when the EC found that the different galenic form of the products in the ATC 3 impacted demand-substitution patterns.

6. *Channel mode*: This variable describes the distribution mode of products in the ATC level 3 category, meaning essentially pharmacy or hospital channels. It takes the value 1 when the channel method of the products in the ATC level 3 class differs and the EC found that it impacted demand-substitution patterns, due to the different buying patterns or reimbursement methods. This variable may partly overlap with the variable representing galenic form. Hospital products differ not only according to their different distribution methods but also, sometimes, have a different galenic form, which may be more appropriate for inpatient care.

7. *Economic regulation in different countries*: This variable describes the different economic regulations

which are often country-specific. It takes the value 1 when the economic regulation differs across products in the ATC level 3 category and leads to changes in demand-substitution patterns.

All the variables are dummies and take the value 1 when the EC considered them to be relevant in explaining substitutability from the demand-side, thus it based its decision specifically on this criterion. Otherwise, it takes the value 0. However, each criterion is not exclusive. For each market definition, the EC may base its decision on one or more criteria so that different dummies may take the value 1 for a specific relevant product market.

In addition to the demand-side substitution variables, the dummy variable "supply-side" takes into account the supply-side substitution patterns. It takes the value 1 when the EC found supply-side substitution patterns relevant and immediate enough to be the basis of the relevant product market definition.

Variables taking into account the specifics of each relevant product market Two variables describing the "number of products with a centralised marketing authorisation at ATC level 3" and the "number of ATC 4 classes" are included in the model in order to take into account the specificity of each particular market in order to reach generalised results.

The first variable corresponding to the "number of products with a centralised marketing authorisation at ATC 3 level", aims to provide an order of the size of the market considered at the ATC starting level 3. It consists of the number of products in the ATC level 3 class having a centralised marketing authorisation. The data use comes from the Community Register of Medicinal Products for Human Use available on the Directorate General for Health and Consumers website [55].

The second variable represents the "number of ATC 4 classes" and corresponds to the number of ATC level 4 classes which exist in the ATC level 3 starting-point, in order to give an overview of the importance and heterogeneity of the ATC level 3 starting-point. The data for this variable was collected from the 2011 version of the ATC classification[56].

Variables taking into account the institutional and political context In addition to these variables, two further variables aim to take into account the institutional and political context surrounding the merger. The first variable, which corresponds to the "turn-over", consists of the logarithm of the global turn-over of the merging firms which is mentioned in the merger decision in the part dedicated to the description of the parties. It aims to investigate whether the turn-over of the merging firms plays a role in the relevant product market definition as decided by the EC.

[55] See Community Register of medicinal products for human use, available at http://ec.europa.eu/health/documents/community-register/html/index_en.htm, last accessed November 2011.

[56] ATC classification 2011 available at http://www.ephmra.org/classification/anatomical-classification.aspx, last accessed February 2011.

The second variable, a dummy, which represents the "merger regulation", takes into account whether the decision happened before the new merger regulation of 2004, or after as the EC's decision regarding the scope of the relevant market may have changed after the adoption and implementation of this new regulation.

From the structure of the ATC classification, the main relevant criteria are expected to be the intended use and the disease gravity which define a broad relevant market at the ATC level 3, based on therapeutic substitution patterns. At narrower scope levels, substitution patterns are expected to be based upon the active ingredient and to vary according to the particularities of the products such as the galenic form or the channel mode.

2.2.2.3 Descriptive statistics on data and discussion

Table 2.2: Description of the variables used

Variable	Obs.	Mean	Std. Dev.	Min.	Max.
Scope of the relevant market	199	.387	.488	0	1
Products with a centralised MA	217	5.018	9.405	0	41
Number of ATC 4 classes	216	2.125	2.378	0	9
Log Turn-over	144	9.800	.825	2500	1716410
Merger regulation	217	.696	.461	0	1
Intended use	202	.698	.460	0	1
Efficacy	202	.079	.271	0	1
Active ingredient	201	.109	.313	0	1
OTC	202	.104	.306	0	1
Galenic form	202	.119	.324	0	1
Channel mode	202	.059	.237	0	1
Economic regulation	202	.0198	.140	0	1
Supply-side	202	.025	.156	0	1

Table 2.2 describes the explanatory and dependent variables used, and shows that, with the exception of the two variables which take into account the specifics of the relevant market under examination and the turn-over of the merging firms, all variables are dummies. The number of observations differs depending on the variables due to the existence of missing observations.

2.2.3 The model

The logit model for binary outcomes is presented at first (2.2.3.1) before explaining the relevance of the ordered logit model in the following econometric analysis (2.2.3.2).

2.2.3.1 Logit model for binary outcomes

Let y_i, which is the scope of the relevant market, be the dependent variable. In a binary response model, y can only take two values.

In this study, the dependent variable can only take two values whether the scope of the market is defined broadly or narrowly. The dependent variable takes the value 0 when the EC's decision defined the market at the ATC level 3, and 1 when the decision defined it at a narrower level (ATC level 4 or even 5).

Let y be the outcome variable and p the probability of the outcome variable $P(y = 1)$. The probability outcome for the observed outcome y can be written $p^y (1-p)^{1-y}$with $E(y) = p$ and $var(y) = p(1-p)$.

Let p_i be the probability that an event occurred for an observation i. The conditional probability can be written $p_i \equiv Pr(y_i = 1|x) = F(X_i\beta)$

$F(.)$ represents a specified parametric function of $x'\beta$ an index function. F is a cumulative distribution function (hereinafter CDF), meaning that $F(-\infty) = 0$, $F(\infty) = 1$ and $f(x) \equiv \frac{dF(x)}{dx} \geq 0$. x represents a regressor vector and β a vector of unknown parameters which is to be estimated (Cameron et al., Chapt.14, pp.446, Davidson et al., pp. 445).

One choice for the cumulative distribution function is the logistic function $\Lambda(x) = \frac{1}{1+e^{-x}} = \frac{e^x}{1+e^x}$. The first derivative of Λ is symmetric around zero so that $\Lambda(-x) = 1 - \Lambda(x)$. The logit model is derived from the assumption that $log\left(\frac{P_i}{1-P_i}\right) = X_i\beta$. By solving for p_i, $p_i = \frac{exp(X_i\beta)}{1+exp(X_i\beta)} = \frac{1}{1+exp(-X_i\beta)} = \Lambda(X_i\beta)$.

To estimate the binary response, the method of maximum likelihood (hereinafter "ML") is the natural estimator (hereinafter "MLE") as the density is the Bernoulli. The MLE solves $\partial lnL(\beta)/\partial\beta = 0$ so that after considerable algebra $\sum_{i=1}^{N}(y_i - \Lambda(X_i\beta))x_i = 0$ (Cameron, 2011). The MLE is consistent if p_i is correctly specified thus $p_i = \Lambda(X_i\beta)$.

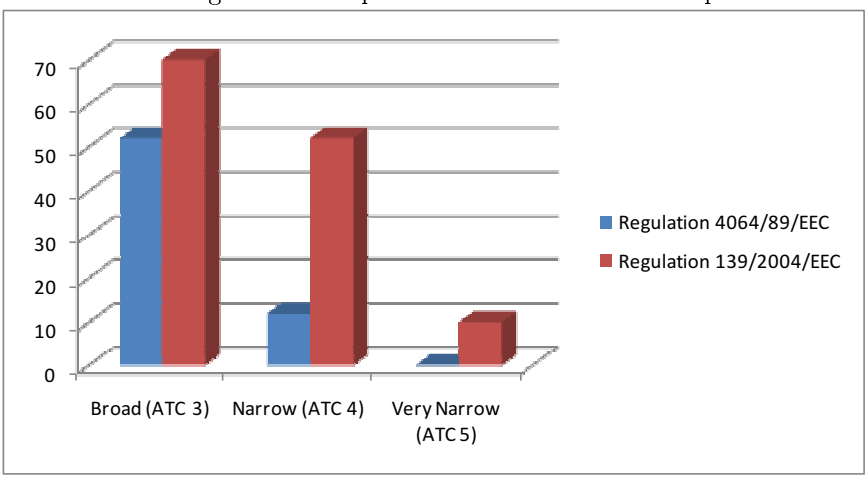
The interpretation of the coefficients is not straightforward as the marginal effects (hereinafter "ME"), which are more informative, have to be calculated. For non linear model such as the logit model, the ME depends on the point of evaluation.

2.2.3.2 Ordered logit model for ordered outcomes

After 2004, the EC defined not only narrow relevant product markets at ATC level 4 or 5 but in some cases specified, whether it considered the relevant market as being the ATC level 5 (molecule level) which is the narrowest market possible or the ATC level 4. This is shown in the figure 2.2.

Trends towards a very narrow market definition from 2004 onward From 2004 to 2011, the EC defined very narrow markets, possibly at the ATC level 5 in nine cases.

Figure 2.2: Scope of the relevant market for pharmaceuticals (1989-2011)



Sources: Data from the sample of mergers analysed

Thus, it may be interesting for the sub-sample of data from 2004 to 2011 to create sub-categories of the resulting narrow markets, whether the EC specified the relevant product market to be at the ATC 4 level (narrow) or ATC 5 level (very narrow).

Indeed, for firms, a definition of the relevant market at the ATC level 5 means that the relevant product market is indeed often the product under consideration, accompanied if its patent already expired, by its generic versions. In such markets defined at molecule level, a product is more likely to be found dominant. In merger cases, the possibility of overlaps decreases when the scope of the relevant market decreases. Hence, it is of interest to know upon which substitution patterns the EC based its decision.

In order to investigate these issues, for the sub-sample 2004-2011, the scope of the relevant product market can be broad (ATC level 3 or even broader), narrow (ATC level 4) or very narrow (ATC level 5) so that the dependent variable is not binary anymore. It takes three values which are ordered in relation to the scope of the relevant market.

Formalising the ordered logit model Cameron et al. (2009, pp. 510) present a model where ordered outcomes arise sequentially as a variable $y*$ attains higher thresholds. In this empirical study, y measures the scope of the relevant market.

For a particular relevant product market, $y_i^* = x_i^*\beta + u_i$ where the regressors x do not include the intercept (normalisation).

For low levels of y^*, the scope of the relevant market is broad. It decreases with higher levels of y^*. For a three-alternative model, it is possible to define, $y_i = j$, if $\alpha_{j-1} < y_i^* \leq \alpha_j$, with $j = 1{,}2\ 3$ and $\alpha_0 = -\infty$ and $\alpha_3 = \infty$. Then, $Pr(y_i = j) = Pr(\alpha_{j-1} < y_i^* \leq \alpha_j$ so that after some transformations,

$Pr(y_i = j) = Pr(\alpha_{j-1} - x_i\beta < u_i \leq \alpha_j - x_i\beta = F(\alpha_j - x_i\beta) - F(\alpha_{j-1} - x_i\beta)$ with F the cumulative distribution function of u_i.

In a logistic model, u is logistically distributed with $F(z) = e^z/(1+e^z)$. The β regression parameters and the two thresholds parameters α_1, α_2 are obtained by maximizing the log likelihood.

The sign of β can be interpreted as determining whether y^* increases with the regressor. The marginal effect on the probability of choosing the particular alternative j when the regressor x_r varies is given by $\frac{\partial Pr(y_i=j)}{\delta x_{ri}} = (F'(\alpha_{j-1} - x_i'\beta) - F'(\alpha_j - x_i'\beta))\beta_r$ (Cameron, 2009, pp. 512)

2.2.4 Empirical results: Estimation and testing of the model

Once results for the sample 1989-2011 have been analysed using the logistic regression (2.2.4.1), the sub sample 2004-2011 is further investigated by using a generalised ordered logit regression (2.2.4.2).

2.2.4.1 Empirical results for the whole period 1989-2011

Logit regression techniques are used to estimate the effect of the various demand and supply-side factors on the scope of the relevant product market while taking into account political and institutional variables as well as the specifics of each relevant market investigated.

Logistic regression and first results After running the first full logistic regression, it may be found, among others, that the regressor's "number of products at the ATC level 3 with a centralised MA" and "turn-over" are not significant. After performing a Wald-test on the coefficient of both variables, with the null hypothesis being the coefficients of both regressors are equal to 0. The result of the Chi-test indicates a p-value equal to 0.4883. Hence, the null hypothesis is not rejected and instead a simplified model is used as the inclusion of the two variables in this model does not lead to any improvement. This result is consistent with the fact that the EC is not influenced by the political context such as the size of the merging firms. In parallel, a model is run with only demand-side substitution variables.

Table 2.3 reports the results of the logistic regression which was performed. It consists of a model 1, including all the regressors except the number of products at the ATC level 3 and the turn-over of the merging firms, and of a model 2, including only demand-side regressors and the dummy corresponding to the merger regulation at the time of the merger.

Both models reveal that all regressors, other than the active ingredient, the galenic form, the economic regulation, and the supply-side factors are relevant. The non-significance of the regressor taking into account the supply-side, is in line with the Commission's Guidelines and the concept of market definition, which emphasises the demand-side substitution factors and only takes into account supply-side substi-

Table 2.3: Logistic regression estimates (coefficients and standard errors)

Scope of the relevant market	Model 1 (coefficients)	Model 2 (coefficients)
Nb of ATC 4 classes	.149 **	
	(.074)	
Merger regulation	1.181***	1.300***
	(.427)	(.421)
Intended use	.835*	.976**
	(.445)	(.434)
Efficacy	3.001***	3.092***
	(.905)	(.886)
Active ingredient	.384	.169
	(.613)	(.577)
OTC	1.357**	1.369**
	(.597)	(.587)
Galenic form	.679	.650
	(.576)	(.565)
Channel mode	1.992**	2.189**
	(.897)	(.889)
Economic regulation	-.936	-.687
	(1.786)	(1.832)
Supply-side	.573	
	(1.230)	
Log-likelihood	-103.113	-105.856
Prob>chi2	0.000	0.000
Pseudo R2	.209	.191
Significance levels	*10%, **5%,	*** 1%

tution patterns when they are immediate. The non-significance of the regressors representing the active ingredient and the galenic form is more surprising and requires further investigation.

The dummy taking into account the change of the merger regulation is highly significant (1% level) meaning that the change in the merger regulation in 2004 has an impact on the scope of the relevant market. The sign of the coefficient is also the sign of the marginal effect.

In order to facilitate interpretation, the marginal effects are calculated and reported in table 2.4.

In both model specifications the variables representing the merger regulation and the efficacy are significant at the 1% level to explain the scope of the relevant product market. In model 1, the probability to define the relevant market under the new merger regulation increases by 28% and up to 31% in the second model specification. When the efficacy criterion is considered as a relevant criterion, the probability to define a narrow relevant market increased by respectively 71% and 73% in model specifications 1 and 2. In the first model, the existence of ATC level 4 categories is significant at the 5% level and increases the probability to define a narrow product market by 35%. The presence of OTC and a different channel mode are significant at the 5% level and both increase the probability to define a narrow product market by respectively 32% and 47% in model specification 1, and 32% and 56% in model specification 2.

Table 2.4: Marginal effects from logit

Scope of the rel. market	Marginal effects Model 1	Marginal effects Model 2
Nb of ATC4 classes	.035**	
Merger regulation	.279***	.307***
Intended use	.197*	.230**
Efficacy	.708***	.730***
Active ingredient	.091	.040
OTC	.320**	.323**
Galenic form	.160	.153
Channel mode	.470**	.517**
Economic regulation	.222	-.162
Supply-side	.135	
Log likelihood	-103.113	-105-856
Prob>chi2	0.000	0.000
Pseudo R2	.209	0.191
Significance levels	*10%, **5%,	*** 1%

The results of the logit regressions and the marginal effects for both models are consistent as the same results in terms of magnitude and significance levels are found.

Comparison and evaluation of the results for both model specifications In both model specifications, the overall-goodness-of-fit which is given by the pseudo R2 is in the same range. It is a bit higher in the first model, which consists of all the variables except for the two which were dropped. In both models, the same variables are significant. The variable regarding the intended use is more significant in the second model. In the first model, the number of ATC level 4 classes is also significant.

The fact that merger regulation is of significance, is an indicator that the EC's criteria for decisions changed after the implementation of the new ECMR. Therefore, it will be important to investigate in more detail later in a sub sample on data for the period 2004-2011.

The overall-goodness-of-fit is also given by the compared predicted probabilities with sample frequencies. With a number of quantiles equal to 10, the result is a p-value equal to 0.371 for the first model and 0.042 for the second model. The outcome of the test does not indicate any misspecification for the first model but some exist for the second one (Cameron and Trivedi, 2009, p. 458). Moreover, by comparing the predicted outcomes with the actual outcomes, it may be observed that 72.82% of the values are correctly specified in the first model and 70.41% in the second one. Hence the decision to work with the first model.

Investigating the effect of the different criteria on the scope of the relevant market Once it is apparent that the model is correctly specified, then it may be investigated how the different criteria,

also in combination, influence the scope of the relevant market defined by the EC.

This analysis shows that the most important criteria are the change in the merger regulation, the presence of first and second generation molecules, the channel model, and the presence of OTC. Over the entire period investigated, the intended use (corresponding also to first or second line treatments) has a lower impact on the scope of the relevant product market than the presence in the ATC level 3 class of first and second molecule generation differing by their efficiency.

As a result, in the presence of two products with a different efficiency, the probability of having a narrow relevant market increases by 63%, while it is only 16% when the products investigated differ by their intended use.

The galenic form of a product does not have an important impact on the relevant market as in the presence of drugs having a different galenic form, the probability of having a narrow market is only of 14%. The presence of OTC has a bigger impact on the relevant market, as, where OTC's are present, the probability of defining a narrow market increases by 25% and up to 52% under the new merger regulation.

Finally, the channel mode of a pharmaceutical changes the definition of the relevant market as the probability of defining a narrow relevant market in the presence of drugs with a different channel mode increases by 39%.

Further investigation of whether the ECMR influences the scope of the relevant market decided by the EC is important as under the new merger regulation, for two products which both differ by their intended use, the probability of defining a narrow market increased by 33%, in comparison to the old merger regulation. Under the latter, the probability of two products differing by their intended use corresponds to 16% and is equal to 39% under the new ECMR.

Conclusions on the first results The hypothesis has been verified, meaning that demand-side substitution patterns are a basis on which the relevant product market may be defined. Specific criteria, such as the channel mode, the presence of a new molecule or of products sold OTC in the ATC level 3 starting-point modify the demand substitution patterns so that they depart from the ATC level 3 and lead to a narrower relevant product market definition. Supply-side criteria do not seem to play a decisive role. Political context does not play role, which confirms the EC's independence. The same conclusion is valid for economic regulation implemented by EU member states. The results concerning the market definition under the old regulation and the ECMR lead us to create a sub sample of the data, in order to better take into account the impact of the ECMR on the EC's approach to define the relevant market.

2.2.4.2 Empirical results for the sub sample 2004-2011

Description of the sub sample For the period 2004 to 2011, the market result is no longer a binary variable, instead it can take three values, 0, 1, or 2, depending on the scope of the relevant market as decided by the EC. The value 0 means that the market was defined broadly (ATC level 3), 1 narrowly (ATC level 4), and 2 very narrowly (ATC level 5). Table 2.5 reports the repartition of the scope of the relevant market from 2004 to 2011. During the period from 2004 to 2011, the number of observations of the dependent variable is equal to 133 as shown in table 2.6.

Table 2.5: Repartition of the scope of the relevant market from 2004 to 2011

Scope of the relevant market	Freq.	Percent	Cum.
Broad	70	52.63	52.63
Narrow	53	39.85	92.48
Very narrow	10	7.52	100.00
Total	133	100.00	

Table 2.6: Description of the variables from 2004 to 2011

Variable	Obs.	Mean	Std. Dev.	Min.	Max.
Market result	133	.549	.633	0	2
Nb. of ATC 4 classes	150	2.293	2.460	0	9
Intended use	136	.596	.493	0	1
Efficacy	136	.088	.285	0	1
Active ingredients	136	.162	.370	0	1
OTC	136	.154	.363	0	1
Galenic form	136	.154	.364	0	1
Channel mode	136	.074	.262	0	1
Economic regulation	136	.015	.121	0	1
Supply-side	136	.022	.147	0	1

Results of the ordered logit regression specifications As the data is naturally ordered according to the scope of the relevant market (broad, narrow, very narrow), the ordered logit model offers a regression (Cf. table 2.7).

The same model specifications are run as previously (model 1 and 3 in table 2.7) and, in addition, a third specification including the demand-side substitution patterns and the number of products at the ATC level 4 (model 2).

The three model specifications converge after three iterations and the Chi2 is found to be significant. All of the coefficients in the three model specifications have the same magnitude and significance with the exception of efficacy, which becomes significant (at the 10% level in the model 2 and 5% in the model 3) and where coefficient increases and the active ingredient looses significance in the third model.

Table 2.7: Results of the ordered logit model

Scope of the relevant market	Model 1 (coefficients)	Model 2 (coefficients)	Model 3 (coefficients)
Number of ATC 4 classes	.117 (.074)	.111 (.073)	
Intended use	.891** (.406)	.906** (.402)	.969** (.395)
Efficacy	.974 (.663)	1.059* (.600)	1.230** (.590)
Active ingredient	1.203** (.544)	1.137** (.533)	.896* (.514)
OTC	.700 (.504)	.678 (.502)	.716 (.529)
Galenic form	.154 (.548)	.209 (.540)	.214 (.529)
Channel mode	1.403** (.661)	1.452** (.653)	1.504** (.657)
Economic regulation	.530 (1.434)		
Supply-side	.651 (1.125)		
Log-likelihood	-105.293	-105.533	-107.826
Prob>chi2	.003	.001	.002
Pseudo R2	.105	.103	.088
Significance levels	*10%, **5%	***1%	

Important criteria in terms of significance and magnitude to define a market at a narrower scope are: intended use, active ingredient, and channel mode.

If the results are then compared with those obtained for the whole period, the number of ATC level 4 classes becomes insignificant in the sub sample 2004-2011 as well as the presence of OTC. However, the active ingredient becomes significant at 5% and 10% depending on the model level with a coefficient which increases.

The results show that during the period 2004-2011, active ingredients become significant which is in line with an analysis at the molecule level due to the presence of generics. It also supports the thesis that the EC tends to define generic-only markets based on the active substance.

Generalised ordered logit model By performing a Brant test[57] of the parallel regression assumptions to verify that the proportional odds assumption is not violated, it is found that it is, indeed, the case.

Based on Williams (2006), a so-called generalised ordered logit model is used for ordinal dependent variables in order to estimate a model which is less restrictive than the ordered logit model. It is also more parsimonious than other non-ordered models, such as the multinomial logistic regression.

[57] In Stata, the Brant test compares the slope coefficients of the J-1 binary logits implied by the ordered regression model and reports the results of an omnibus test for the whole model and tests the assumption for each of the independent variables present.

The generalised ordered logit model can be written as $P(Y_i > j) = g(X\beta_j) = \frac{exp(\alpha_j + X_i\beta_j)}{1+[exp(\alpha_j + X_i\beta_j)]}, j = 0, 1, 2$ corresponding to the categories of the ordinal dependent variable. The ordered model is a special case of the generalised ordered logit model where the β are the same for all j[58].

Results of the generalised ordered logit model A statistic of 0.0619 is perceived which is insignificant, thus the final generalised ordered model does not violate the parallel line assumption. Similar results to the ordered logit model are found concerning the significance of the regressors.

Regressors have the same significance in both models' specifications even if, in the second model with only demand-side substitution variables, the magnitude of the coefficients is greater on average. The significance of the intended use in the first panel is also very high (1% level).

In order to interpret the results of the general logit regression, it is important to keep in mind, that the effect of a variable depends on the scope of the relevant market. This means that the effects of an explanatory variable will not be the same across two cumulative logits of the model. Gologit coefficients can be interpreted as coefficients from binary logit models, where the categories of the outcome variable have been collapsed into two categories (Williamson, 2006). The first panel of coefficients can be interpreted as stemming from a binary logit regression where the dependent variable is recoded as 0 (broad scope) versus 1+2 (narrow and very narrow scope). The second panel of coefficients can be interpreted as stemming from a binary logit regression where the dependent variable is recoded 0+1 (broad and narrow scope) versus 2 (very narrow scope).

Thus, the second panel is particularly interesting as it provides significant criteria in defining very narrow markets. Coefficients can be positive or negative. Positive coefficients mean that higher values of the coefficients make it more likely that the dependent variable takes higher values. If this is applied to the regression, a positive coefficient makes it more likely for the relevant market to be narrowly defined. For the second panel, the results differ as the efficiency becomes insignificant, whereas the presence of OTC becomes significant as well as the galenic form. Furthermore, taking into account the active ingredient, the regressor becomes highly significant at the 1% level.

The effects of the constrained variables (number of ATC 4 classes, intended use, OTC, and channel mode) can be interpreted in the same manner as in an ordered logit model. Of the constrained variables in the first model, two are significant at the 5% level, intended use (1.06) and channel mode (1.4). Whereas in the non-constrained variables, the variable efficacy is significant at the 0.05% level, with a coefficient

[58] In STATA, the command "gologit2" allows for an estimation of a partial proportional odds model, where the constraint concerning parallel lines is only relaxed for the variables where it is not justified. The command "autofit" allows the parallel line assumption to be relaxed where the assumption is violated. A totally unconstrained model is first estimated and tested for each individual variable whether it meets the parallel line assumption. The model is then estimated the model with constraints. Lastly, a global Wald test of the final model with constraints versus the original model unconstrained is performed.

Table 2.8: Results of the generalised ordered logit regression

Log likelihood=-97.820807 Pseudo R2=0.169

Market result	Model 2	Model 3
0		
Nb. of ATC 4 classes	.114	
	(.759)	
Intended use	1.061**	1.135***
	(.423)	(.415)
Efficacy	1.915**	2.056**
	(.846)	(.840)
Active ingredient	.577	.367
	(.562)	(.537)
OTC	.883*	.918*
	(.535)	(.531)
Galenic form	.105	.131
	(.567)	(.560)
Channel mode	1.417**	1.521**
	(.706)	(.711)
1		
Nb. of ATC 4 classes	.114	
	(.759)	
Intended use	1.061**	1.135***
	(.423)	(.415)
Efficacy	-9.580	-.715
	(1.232)	(1.184)
Active ingredient	3.334***	3.190***
	(.910)	(.903)
OTC	.883*	.918*
	(.535)	(.531)
Galenic form	2.130**	2.100**
	(.992)	(.988)
Channel mode	1.416**	1.521**
	(.706)	(.711)
Log-likelihood	-97.821	-99.820
Prob>chi2	.000	.000
Pseudo R2	.168	.156
Significance levels	*10%, **5%	***1%

1.9 to narrow the scope of the general market and becomes insignificant in defining narrower markets in particular. On the other hand, the variables representing the active ingredient and the galenic form, which are not significant to define narrow markets become significant respectively at the 1% and 5% level with a respective coefficient of 3.33 and 2.13 to explain a very narrow scope of the relevant market. The coefficients of the non-constrained variables are nearly double the coefficient of the constrained variables.

Investigations regarding the scope of the relevant market in the sub sample 2004-2011 in the ordered logit and generalised ordered logit model A conclusion may be drawn from the results of the ordered and generalised ordered logit models, that some regressors tend to be important criteria in decreasing the general scope of the relevant market, either at narrow or very narrow levels. This is particularly the case of the intended use and channel modes.

Other criteria tend to be only significant in defining very narrow markets, meaning at ATC level 5. This is the case in the presence of OTC and when the galenic form and the active ingredient are relevant. The inclusion of OTC in these criteria seems surprising at first sight but this can be explained by the specifics of the ATC classification. It is fairly often the case that OTC and on-prescription medicinal products are grouped together at the ATC levels 3 and 4 so this differentiation only happens at the ATC level 5.

Marginal effects in the generalised ordered logit model In a secondary step it is important to analyse the marginal effects which are easier to interpret than the generalised ordered logit coefficients.

A marginal effect (hereinafter ME) measures the effects on the conditional mean of the explained variable, here "market result", on a change of one of the regressors. In a linear model, it is equivalent to the slope of the coefficient meaning that $\beta_j = \partial E(y \mid x)/\partial x_j$. This is however not the case in non-linear models such as logit and ordered logit models as the marginal effects differ depending upon the point of evaluation.

Table 2.9 evaluates by default at the sample mean $x = \bar{x}$ in order to get the MEM[59]. For binary regressors, which is the case in this regression, ME are calculated using the finite difference[60].

ME in the first panel The first panel of marginal effects shows that when factors taking into account the channel mode and the efficacy of the product are found to be relevant by the EC, the

[59] In non-linear models marginal effects differ according to the point of evaluation. Three marginal effects are of interest, the marginal effect at representative value (MER), the average marginal effect (AME), and the marginal effect at mean (MEM). Based on Cameron and Trivedi (2009, p. 340), the MEM is the best indicator to provide a rough order of the magnitude of the marginal effects.

[60] The command "mfx2" in STATA is used with the generalised ordered logit model.

Table 2.9: Marginal effects of the generalised ordered regression

Market result	Coefficients
0	
Intended use	-.274**
Efficacy	-.422***
Active ingredient	-.091
OTC	-.223*
Galenic form	-.033
Channel mode	-.338***
1	
Intended use	.241***
Efficacy	.439***
Active ingredient	-.207*
OTC	.184*
Galenic form	-.107
Channel mode	.249***
2	
Intended use	.033*
Efficacy	-.017
Active ingredient	.299**
OTC	.039
Galenic form	.139
Channel mode	.090
Significance levels	*10%, **5%; ***1%

probability for the market definition to be defined at the ATC level 3 decreases (-0.42 and -0.34 for respectively) at 1% level significance. The intended use (-0.27) is also relevant at the 5% level significance.

ME in the second panel In the second panel, some factors influence the probability of defining the relevant market at ATC level 4. This is the case when efficiency (+0.44), intended use (+0.24) and channel mode (+0.25) at 1% significance level are found to be relevant, as well as the presence of OTC (+0.25) at a 10% significance level. The marginal effect for the active ingredient is negative (-0.21) at a 10% significance level which means it has a negative effect on the probability to define the relevant market at ATC level 4.

ME in the third panel Finally, in the third panel, factors which influence the probability that the EC defines the relevant market at the ATC level 5 are the active ingredient (+0.30) at 5% significance level, and at a lower level intended use (+0.03) at 10% significance level.

Comparison of the different model regressions By comparing with the results found in the ordered and generalised ordered logit regressions, the importance of the intended use and the channel mode are reiterated to define narrower markets. More specifically, with regards to factors leading to the definition of very narrow markets, the importance of the active ingredient is emphasised.

The galenic form is found not to be significant in any of the panels, which differs from the results of the ordered and generalised ordered logit regressions, but is in line with the results of the logistic regression over the whole period from 1989-2011.

Conclusions of the different model regressions The results support the hypothesis that demand-substitution patterns are important determinants in defining the scope of the relevant market in the full data sample from 1989-2011, as well as in the sub-sample from 2004-2011. Furthermore, while the intended use is the general criterion employed to decrease the scope of the market definition, either at a narrow or a very narrow level, specific key factors in defining very narrow markets are the active ingredient and channel mode.

The results from the different model regressions also lead to the conclusion that some key specific factors are important in defining very narrow markets. While the intended use is the main criterion which explains the EC's choice to decrease the scope of the relevant market, the active ingredient, the channel mode, and specifically the galenic form are key criteria to define very narrow markets at the molecule level. The efficacy of a product is important in order to narrow the relevant market at the ATC level 4, but not at a narrower level. The presence of OTC also increases the probability of defining market

definition at ATC level 5. It may be seen however that this result comes from the peculiarities of the ATC classification which often differentiates the OTC from on-prescription medicines only at a very narrow level and not already at the ATC level 3.

These empirical results recoup the main distinctions which were made by competition status (corresponding to the active ingredient), the prescription status (presence of OTC) and the way of distribution (channel mode and due to the specific demand of hospitals, the galenic form).

Discussion and points for future research This study had two main objectives. The first was to review, in an empirical way, which criteria were used by the EC to define the scope of the relevant market and particularly the criteria which justifies departing from the ATC level 3 (therapeutic substitution). The second objective was to investigate whether the EC tended to define narrower markets and if so, which were the important criteria in defining a very narrow market at the molecule level (ATC 5). Results of the key criteria investigated and their impact to narrow the scope of the relevant market can be summarised as follows:

- Efficiency (= presence of molecule of different generations) –> ATC level 4
- Active ingredient and galenic form (= dosage, route of administration...) –> ATC level 5
- Intended use, presence of over-the-counter products and channel mode (= pharmacy or hospital channels) –> indifferently ATC level 4 or 5

This trends towards defining narrower markets over time can be explained by two main reasons. The first main reason is of procedural nature and results from the changes brought by the new ECMR in 2004, and in particular the increased use of economic analysis in the merger review performed by DG COMP. It corresponds among others to the establishment of a Chief Economist team in charge of giving economic guidance and methodological assistance in the ongoing investigations as well as providing an independent opinion. This more economic approach developed by DG COMP also takes the form of the "Significant Impediment of Effective Competition" (SIEC) test where the focus is put on effective competition rather than the market structure. The second main reason is of business nature. Pharmaceutical markets are evolving and characterized by many fusions leading to the presence of a small number of key players active worldwide with a broad portfolio of medicinal products and pipeline products in various therapeutic areas. Moreover, the regulatory framework can drive the research towards certain areas. As an example, the orphan drug legislation in the EU which was introduced in 2000 with the aim to stimulate the research and development of orphan drugs, provides financial and non-financial incentives for the development of

orphan medicinal products.The concentration of research in certain therapeutical areas might be a reason to explain the trends towards narrower markets over time.

In future studies, it may be of interest to include in the sample not only mergers where the market was defined with reference to the ATC classification, but also to other classifications such as the EDMA classification for companion diagnostics. It would however become necessary to find a common unit scale between both classifications. Such a study would gain in significance due to the inclusion of more relevant markets. This would also be of interest due to the increasing importance of the diagnostics industry.

CONCLUSION OF CHAPTER 2

The definition of the relevant market for pharmaceuticals is not straightforward. In its approach, the EC defines the relevant product based on demand-side substitution patterns.

The main criteria found which explains the departure from a classification based on therapeutic substitution patterns are intended use, efficiency, channel model, and prescription status of products. Some specific criteria tend to narrow the scope of the relevant market to molecule markets. This is the case for active ingredient, channel mode, galenic form, and the prescription status of pharmaceuticals. These criteria overlap the distinction of pharmaceuticals by competition status, by means of distribution, and by prescription status.

While the definition of the relevant product market for pharmaceuticals is a case-by-case analysis, the above-mentioned criteria should be seen as key indicators in defining markets based on demand-substitution patterns. Therefore, this analysis has implications beyond the definition of the relevant market in merger and dominance investigations. The demand-substitution criteria which were defined are also useful to analyse and further cluster products based on demand-substitution patterns. Cost-containment measures such as internal or external reference-pricing or regulations concerning generics often require clustering products together, dependant upon their substitutability for the patient in order to promote a cost-efficient prescription.

Chapter 3

REFERENCE PRICING AND ITS IMPACT ON INNOVATION INCENTIVES

ABSTRACT OF CHAPTER 3

After the patent expiry of an originator medicinal product, economic theory predicts that price competition should be heightened due to the arrival on the market of generic versions. However, the presence of health insurers playing the role of third payers as well as the presence of an information advantage which takes the form of brand loyalty and brand recognition in favour of originator medicinal products, result in impeding the normal functioning of price competition as the off-patent originator has a headstart.

Consequently, an internal reference pricing scheme which increases the elasticity of demand above the reference price set, is one of the main instrument used to promote generics and to counterbalance the impact of an information advantage.

In this chapter, the objective is to investigate the impact of internal reference pricing on the pharmaceutical companies' incentives for innovation in the presence of an information advantage.

Once reference pricing schemes have been defined, follows an analysis of how a reference pricing scheme works in the presence of information imperfection in order to increase the price elasticity of demand, and its impact on prices, profits and innovation incentives. In a third and final part, the focus is on the role of reference pricing on incentives to innovate and on its subsequent impact.

Following a review of the different substitutability levels and substitutability patterns through the definition of the relevant product market, the aim of this third chapter is to study one widely used cost-containment measure: internal reference pricing. This is one of several measures, mainly affecting off-patent markets, which aims to increase price competition among products grouped in a same cluster. The closer the possible substitution among products within the cluster, the higher the resulting price-competition. However, such barriers to price competition exist due to an information advantage in favour of off-patent originators which discriminates against generic versions. Such measures, when focused upon non-innovative medicinal products, also indirectly have consequences on innovative medicinal products.

In the next section (3.1) the mechanism of reference pricing is reviewed, so that its functioning may be modeled by taking into account the information advantage which exists in favour of the originator product and how this empirically falsifies price competition and tends to further decrease price elasticity in health markets (3.2). Based on these results, the impact of reference pricing on innovation incentives is also analysed in a theoretic model (3.3) and policy implications are drawn regarding the use of such schemes with particular reference made to examples of Germany and France (3.4).

3.1 Functioning of internal reference pricing

Reference pricing is a widely used measure employed in order to foster price competition in off-patent markets. First, it is necessary to explain how reference pricing functions (3.1.1), the different features of reference pricing will then be described (3.1.2) and some experiences in Germany and France presented (3.1.3). Finally, the theoretical and empirical literature on reference pricing are reviewed (3.1.4).

3.1.1 Definition of internal reference pricing

When setting a reference price, internal reference pricing is first and foremost a reimbursement rule (3.1.1.1), the objective of such a scheme is to promote price competition among medicinal products in off-patent markets (3.1.1.2).

3.1.1.1 Reference pricing as a reimbursement rule

When a consumer buys an on-prescription drug at the pharmacy, the full costs of the product are not borne out-of-pocket, as health insurance funds pay the rest. The copayment may be based on a percentage rate of the price of the product, or may consist of a fixed amount of the product's price (Economic Papers, 2012).

Setting a reference price assumes the attribution of a maximum price which will be reimbursed. By implementing a reference price system, health authorities cluster drugs according to equivalence criteria and thus define a reference price. The underlying assumption is that the products included in the cluster are substitutable. Below the reference price, usual copayments apply, whereas above the reference price, the patient has to pay the remainder out-of-pocket. Reference pricing is used as a cost-containment measure mainly for off-patent medicines with generic competition and more rarely for medicines still on-patent.

Formal definition of internal reference pricing Formally, by defining P as the price of the medicine, $\bar{P}$ as the reference price, P_C the price paid by patients and θ as the copayment rate, the result in the presence of a reference pricing scheme is:

$$P_C = \begin{cases} \theta\bar{P} \; if \; P < \bar{P} \\ (P - \bar{P}) + \theta\bar{P} \; if \; P > \bar{P} \end{cases}$$

More concretely,

- Example (1): For a price of $P = 10$, a copayment rate of 10% and a reference price $P_{RP} = 8$, the consumer has to pay out-of pocket $P_C = (10 - 8) + 0,10 * 8 = 2,80$
- Example (2) : For a price equal to the reference price $P = P_{RP} = 8$, a copayment rate of 10%, the consumer has to pay out-of pocket $P_C = 0,1 * 8 = 0,8$

Consequently, when the price of the drug is equal to, or below the reference price, only the usual copayment applies. When the ticket price of the medicine is higher than the reference price set, the patient has to pay, in addition to the usual copayment, the full difference between the ticket price and the reference price.

Internal and external reference pricing Internal reference pricing shall be differentiated from external reference pricing (also called "international reference pricing" or "external price benchmarking"). International reference pricing consists of pinning the price of a drug in one country to the price of the same medicine in a selection of other countries (ESMT White Paper, p. 34) . While it is currently used in 24 out of the 28 member states in the EU, the practices of international reference pricing vary significantly across member states, as they tend to select the benchmark countries based on specific criteria such as geographic or economic factors.

While an international reference pricing concerns the same product in different countries, an internal reference pricing requires to create a cluster of products for cost-containment purposes deemed to be

sustitutable for the patient. This issue of substitutability for the patient has been analysed in the previous chapter from a antitrust point of view with the definition of the scope of the relevant product market and the use of the ATC classification. For that reason, the following part exclusively focuses on internal reference pricing.

3.1.1.2 Reference pricing and promotion of cost-effective pharmaceuticals

For the duration of the patent, the incumbent is alone within a certain specific segment. After patent expiry, bioequivalent generics enter the market and thus exert price competition which was previously nonexistent. The degree of competition between the off-patent originator product and its generic versions is a function of the therapeutic substitutability between products.

As mentioned in the first introductory chapter, price competition is lowered, however, by the presence of health insurers bearing a significant part of the costs and being the final payers, and by the existence of brand loyalty and brand recognition for the originator product. The latter which were alone on the market due to patent protection have an information advantage as originator companies have invested during this exclusivity period by means of targeted advertising to prescribing physicians, consequently increasing brand loyalty towards their products. Advertising enables manufacturers of the originator product to retain large market shares compared to lower price alternatives.

Reference pricing aims to control expenditures of on-prescription drugs and to achieve a cost-effective prescription. Though it does not set the final price, the reference pricing scheme provides firms with incentives to adapt their prices to the reference price set. Hence, it promotes price competition between substitutable products. If the firm does not revise the price of its product downwards, the patient will have to pay the full difference between the ticket price and the reference price on top of the usual copayment. Patients have then an incentive to buy another drug which is cheaper and at a ticket price set equal to or under the reference price level in order to pay only the mandatory usual copayment.

The implementation of a reference pricing system increases the out-of-pocket payments for patients who choose to take high-priced products. The policy's objective is to increase price elasticity of demand for on-prescription pharmaceutical products and stimulate price competition between therapeutically equivalent products after patent expiry.

Rationale of reference pricing The rationale behind reference pricing lies in the characteristics of pharmaceutical markets. Kina and Wosinska (2009) investigated the characteristic patterns which influence the pricing of pharmaceuticals and decrease demand elasticity in these markets and are a reason for the implementation of a reference pricing scheme. They defined four specifics within pharmaceutical

markets.

First of all, the patient does not choose their medication when it is available on-prescription. This role falls upon a prescribing physician to determine the appropriate treatment. This agency relationship may lead to a discrepancy if, for a given disease, the patient would prefer to take the cheapest treatment while in the physician's opinion an alternative may represent a better treatment. This may happen in particular when a product has been heavily advertised, or due to the habits of the prescribing physician.

Secondly, a discrepancy between the price and the real costs for the patient exists due to the fact that health insurers are indeed the final payers. Patients are not confronted with the real price, only the copayments.

Thirdly, the patent system enables firms to price their products higher and to enjoy a certain degree of market power. Consequently, the degree of competition may also depend upon the patent status.

Finally, in most countries, the price of pharmaceuticals is regulated. This heavy regulation is due to the role of national health insurance as payer and the political importance of healthcare. For all of these reasons, prices in the pharmaceutical industry differ from marginal cost. In this specific context, reference pricing is a means to raise the awareness of physicians and patients on the price of the products above the reference price and hereby to counteract the effect of health insurance and advertising on demand price elasticity.

Danzon et al. (2011) investigated the role of regulation and competition in off-patent markets in the US and in the EU. They showed that the extent of savings realised with generics depends on the generic entry and their price levels. The situation in the US is very different in this regard from the situation in the EU. They found that in the US, pharmacists are the key decision makers and have incentives to deliver generic versions to patients. This is due to the fact that pharmacy chains are allowed according to legislation and can buy generics through centralised purchasing. These incentive structures lead to a quicker uptake of generics and, at the same time, a fierce price competition among them.

Contrary to the US, member states in the EU, such as Germany and France[1] can be best described as "physician-driven countries", as physicians are the key decision makers. In these countries, generics compete mainly through brand ("licensed generics", or "authorised generics") and not price competition, leading to higher generic prices. Licensed generics consist of generic versions of an originator product which is indeed manufactured by the originator company, or by a company belonging to the originator company. Incentives for substitution in these countries are often low as, for example, substitution is only allowed when the physician has prescribed using the International Nonproprietary Name (so-called "INN").

[1] Danzon et al. (2011) include i.a. as physician-driven countries France, Germany, Italy, Spain, Japan, Brazil and Mexico (p.7).

This low substitution rate also finds its origin in the fact that the pharmacy dispensing fee increases with the price of the product. Pharmacists lack incentives to deliver cheaper generic version.

It is in this specific context that policies were adopted to promote the prescribing and delivery of cheaper generics such as the system of reference pricing in Germany, in 1989.

3.1.2 Features of reference pricing schemes

Reference pricing exists in more than twenty member states in the EU, but with different structures and features depending on the criteria for defining groups (3.1.2.1), for setting the reference price (3.1.2.2) and on the frequency of update, as well as on the incentives offered to physicians and pharmacists (3.1.2.3).

3.1.2.1 Criteria for defining groups

A reference price applies to a group of products which are clustered according to their therapeutic substitutability. There are different degrees of therapeutic substitutability depending on their level within the ATC classification system[2]. The closer the degree of substitution between products within a group, the higher the level of competition between products.

Lopez-Casasnovas et al. (2000) reviewed the different reference pricing systems in the EU and found three existing levels to define the clustering criteria (Cf. table 3.1).

Generic reference pricing The first level, "generic reference pricing", corresponds with the sole inclusion in the reference price group of the originator product and its generic versions. Substitution is therefore based at the chemical level. This level corresponds to the closest competition level as generics are bioequivalent to their off-patent originator.

Therapeutic reference pricing The second level corresponds with the clustering of products based on pharmacological properties. The third and final level corresponds with the clustering of pharmaceuticals according to their therapeutic equivalence. Therefore, products which treat the same disease with different modes of action and potentially different side effects may be grouped together. The second and third levels of reference pricing correspond to therapeutic reference pricing.

These three levels partly correspond with the different levels of the ATC classification system: ATC 3 (therapeutic), 4 (pharmacological) and 5 (chemical) which were analysed in the second chapter. Clusters based on therapeutic substitution patterns may contain on-patent medicinal products depending on the legislation. Taking Germany as an example, patented products that have been recognised as offering an

[2]Cf. Chapter 2 on the definition of the relevant product market.

Table 3.1: Three levels for clustering products in reference price groups

	Levels of equivalence	Corresponding ATC level
First level	Chemical: Corresponds to a reference price group with the same active ingredient	ATC level 5
Second level	Pharmacological: Corresponds to a reference price group with products in the same therapeutic category	ATC level 4
Third level	Therapeutic: Corresponds to a reference price group with products having the same therapeutic function	ATC level 3

Sources: Lopez-Casanosvas et al., 2000, p. 109

insufficient improvement, when compared to possible alternatives, can be included in a reference price group.

Lopez-Casasnovas et al. (2000) showed how this generic reference pricing scheme creates the most homogeneous group, as products in the cluster are close substitutes, unlike therapeutic reference pricing which leads to the most heterogeneous groups. In these bigger clusters, products are imperfect substitutes, so that they may not be fully interchangeable, especially in terms of side-effects, indications, dosage, bio-availability (i.e. in terms of fast or slow action) or galenic form. Lopez-Casasnovas et al. explained how special safeguards have been implemented in the patients' interests, such as in British Columbia where patients are fully reimbursed above the reference price if the prescribing physician can justify this prescription choice for higher-priced products.

In eleven EU member states such as Belgium, Italy, and Slovenia, clustering of products in reference groups is performed at the molecule level, i.e. at ATC level 5. In other countries, such as Germany, the Netherlands, and Poland, reference pricing groups are defined at broader levels, such as ATC level 4 or even ATC level 3 (ÖBIG, PPRI Report 2008). This is shown in figure 3.1.

3.1.2.2 Criteria for setting the reference price

Once the reference price group has been defined, an important criterion consists of defining the level of the reference price. In practice, the price may be the lowest price of the product in the group, the average, or the median price of the products included in the cluster.

The reference price level is important as it determines the extent of potential savings for health insurers. The lower the level at which the reference price level is set, the higher the savings which can be achieved. In some countries, the reference price is set according to specific calculations. Thus, in Germany, the reference price corresponds to the lowest third of products contained in the group, while in the Netherlands it corresponds to one half.

Figure 3.1: Overview of internal reference pricing in the EU

	Internal reference pricing		
	Clustering	Pricing	Updates
Austria	-	-	-
Belgium	ATC-5	31% below original	Every 6 months
Bulgaria	ATC-5 and 4	Lowest price	n.a.
Cyprus	-	-	-
Czech Republic	ATC-5 and 4	Lowest price	Every 6 months
Germany	ATC-5 and other levels	Combination of prices	Minimum once a year
Denmark	ATC-5	Lowest price	Every two weeks
Estonia	ATC-5	Lowest price	Quarterly
Greece	-	-	-
Spain	ATC-5	Avg. of the lowest 3 prices	n.a.
Finland	ATC-5	Lowest price plus a flat amount	n.a.
France	ATC-5	Lowest price	n.a.
Hungary	ATC-5 and 4	Lowest price	Annually
Ireland	-	-	-
Italy	ATC5, 4 and 3	Lowest price	Monthly
Lithuania	ATC-5	Lowest price	n.a.
Latvia	ATC5, 4 and 3	Lowest price	n.a.
Luxembourg	-	-	-
Malta	-	-	-
Netherlands	ATC-4	Avg. price or below	n.a.
Poland	ATC5, 4 and 3	Lowest price	n.a.
Portugal	ATC-5	Avg. of the lowest 5 prices	Quarterly
Romania	ATC-5	Lowest price	n.a.
Sweden	-	-	-
Slovenia	ATC-5	Lowest price	Every 6 months
Slovakia	ATC5 and 4	Lowest price	Quarterly
United Kingdom	-	-	-

Sources: EU, Economic Papers, 2012

In Denmark, Slovakia and Hungary, a form of auction process takes place to set both the price and reimbursement level, creating a dynamic in the system. In Slovakia for example, pharmaceutical firms communicate their price to the Ministry of Health which publishes them on their website. Within a two week period, pharmaceutical firms can offer another price which can be lower than the first one. This second proposal is considered as final by the Ministry of Health which uses it as a reimbursement basis. This mechanism creates competition at ATC level 5 (Leopold et al., 2008, p.8).

The reference price should also be based on a common unit for delivery across the products in the cluster. Two dominant approaches may be observed (Leopold et al., 2008, p.7): the price may be based on one unit of the product, as is the case in Denmark or Portugal, or based on the Defined Daily Dose[3] (hereinafter, DDD), as is the case in Belgium, the Netherlands and Slovakia.

3.1.2.3 Frequency of update

The frequency at which the reference price is updated is also an important feature of the reference pricing scheme. In some countries such as Belgium, Slovenia and the Czech Republic, the reference price is updated every six months while in Estonia, Portugal, and Slovakia, an update takes place each quarter (Leopold et al., 2008, p.8) .

While a more frequent update of the reference price tends to increase the potential savings for the

[3]The defined daily dose (DDD) is a measure of drug consumption defined by the World Health Organization in order to allow for drug usage comparisons between different drugs.

health insurer, it also leads to more administrative work.

Incentives given to physicians and pharmacies to substitute products are key for the reference pricing to succeed. Physicians and pharmacists are offered both financial and non-financial incentives to prescribe and dispense cheaper products.

Hence, the less substitutable products are within the cluster, the more unlikely it is that physicians and pharmacists will substitute them.

3.1.3 Experiences of reference pricing in the EU - Examples from Germany and France

Germany was the first country in the EU to introduce a reference pricing system on 1 January 1989 as a means of regulating prices[4]. This was followed by the Netherlands which introduced a reference pricing system in 1991, and Sweden and Denmark in 1993. France introduced a certain form of reference pricing in 2004 by implementing the "Tarif Forfaitaire de Responsabilité" .

Currently, as shown in figure 3.2 twenty-four out of the twenty-eight member states have adopted a reference pricing system, but different features exist in each country. The reference pricing schemes in Germany (3.1.3.1) and France (3.1.3.2) are very different.

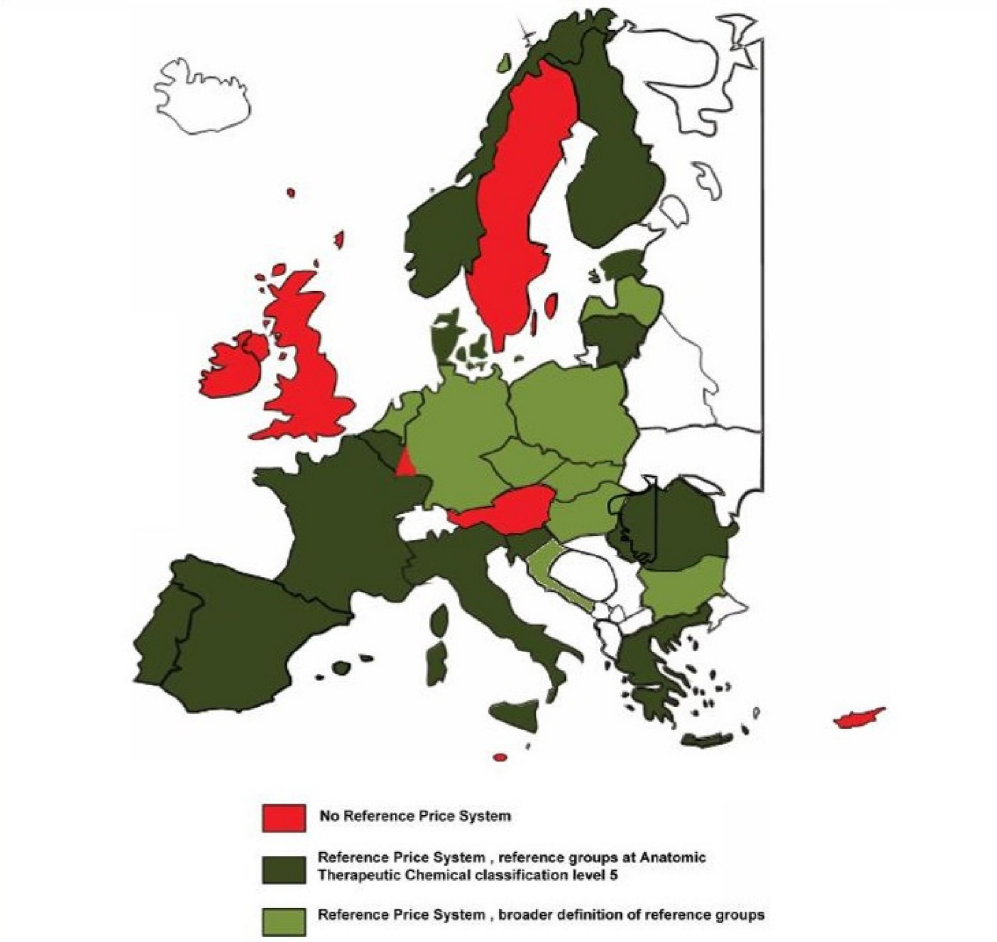
3.1.3.1 Germany

Creation of "Jumbo reference groups" The Federal Joint Committee G-BA [5], which consists of representatives for physicians, hospitals, and also health insurance funds, is in charge of grouping products in clusters (so-called "Festbeträge"), which takes place on the basis of three levels. The first level corresponds to products containing the same active ingredients, the second level to products with pharmaco-therapeutically comparable active ingredients, and the third level to products with comparable therapeutic effects, especially combined products. An active ingredient can be included in a reference price group only if therapeutic alternatives exist[6].

This form of cluster may therefore contain both off-patent originators and generic drugs. However, products with different administration modes are never clustered in the same group. Patented products were included in the reference pricing scheme from 1989 to 1996 and re-introduced in 2004 in the Health Insurance Modernisation Act (so-called "GKV-Modernisierungsgesetz"). Excluded from the reference pricing scheme are products, where the : " mode of action is innovative or which represents a therapeutic

[4]Cf. Art. 35 of the Sozialgesetzbuch V (SGB V) available at http://www.gesetze-im-internet.de/sgb_5/__35.html, last accessed August 2012.
[5]Cf. website of the G-BA, http://www.g-ba.de.
[6]Cf. Art. 35 Par. 1 S. 3 SGB V.

Figure 3.2: Reference pricing in Europe (2012)



Sources: Generics and Biosimilars Initiative Journal, 2012

improvement, also due to lower side-effects"[7].

New products which do not show any improvement, in terms of effectiveness over existing alternative treatments, are included in the reference pricing scheme, creating so-called "jumbo groups".

Setting the reference price The federal association of health insurers (so-called "GKV-Spitzenverband") is in charge of setting the reference price level in each group. Below the reference price, patients have to pay a copayment which is between €5 and €10 depending on the price of the drug. However, when the price of the product is at least 30% lower than the reference price in the cluster, the product is free from the copayments.

The reference price is calculated by taking the average of the three lowest priced drugs in the cluster and by adding one third of the difference between the average of the three highest priced and lowest priced products.

As the reference price has to correspond with the actual state of the medical knowledge available, reference prices are regularly updated[8].

Incentives for stakeholders Reference pricing is not the only cost-containment measure in Germany as price cuts, price freezes, price ceilings, discounts, and rebate contracts are also implemented. In 2010, according to the GKV-Spitzenverband, the reference pricing system enabled savings of around €4.6 million (GKV-Spitzenverband, 2011). Around 73% of the prescriptions written by physicians in 2011 concerned reference priced products which corresponded to 42% of the turn-over of pharmaceuticals reimbursed by mandatory health insurance (so-called "GKV-Arzneimittelmarkt").

Since 2002, pharmacists can substitute off-patent originators for generics within the reference price group, as long as the generic version belongs to the three cheapest prices in the cluster and the physician has not explicitly forbidden substitution. Thus, pharmacists benefit from incentives to deliver generics as, on average, they have a margin of 36% on the delivery of a generic medicine (Generic Bulletin, 2010). With the growth of tendering procedures as launched by public health insurers (so-called "Rabattverträge"), the pharmacist's choice is restricted.

3.1.3.2 France

Introduction of the Responsible Payment Tariff ("Tarif Forfaitaire de Responsabilité", hereinafter TFR) In France, the Responsible Payment Tariff (TFR) was modeled on the Germany's

[7] Cf. Art. 35, SGB V, "Ausgenommen von diesen Gruppen sind Arzneimittel mit patentgeschützten Wirkstoffen, deren Wirkungsweise neuartig ist oder die eine therapeutische Verbesserung, auch wegen geringerer Nebenwirkungen, bedeuten".

[8] Cf. Art. 84 Par. 5 of the SGB V with regard to the actualisation method of the reference price and Art. 43 of the Guidelines of the G-BA (so-called "Arzneimittelrichtlinie") and in chapter 4 Annex I Par. 6 of the Code of procedure of the G-BA.

reference pricing system, while taking into account the specifics of the price-setting of medicinal products in France. While in Germany, price-setting used to be free, price-setting of medicinal products in France is regulated. Prices of medicinal products are set by negotiations between the pricing committee CEPS, and the pharmaceutical company for four years[9]. Price of the generic is 60% lower than the price of originator. The TFR was introduced by the Social Security Financing Law 2003 (so-called "Loi de Financement de la Sécurité Sociale")[10] for generics with a penetration rate in the French market lower than 45% of the sales of the off-patent originator. In 2010, 850 products were concerned out of the 1850 medicinal products reimbursed[11]. This tariff consists of a maximum reference price which applies to both off-patent originators and generics.

Impact of the TFR France, historically, has a lower penetration rate of generics than other EU countries, such as Germany.

The TFR was implemented to support the introduction of the right given in 1999 to pharmacists to substitute an originator product by its generic version, or the generic version of a product by another cheaper generic version[12]. The TFR supplements the objective to promote the uptake of generics in France. Financial incentives, through margins and discounts, were also given to ensure the delivery of generic by pharmacists.

3.1.4 Review of the literature on reference pricing

Economic studies on reference pricing schemes mainly analyse the impact of reference pricing on expenditure, health outcomes of patients, and the resulting incentives to innovate. While theoretical works were published (3.1.4.1), the existing literature remains mostly empirical (3.1.4.2).

3.1.4.1 Theoretical literature on reference pricing

Economic papers which investigated the impact of reference pricing on different variables use the same general framework of a vertical and/or a horizontal differentiation model, for instance, a Hotelling framework.

In a therapeutic reference pricing, which groups products based on similar therapeutic indications, a horizontal differentiation exists between the different therapeutic products included in the cluster, because

[9] For more details, cf. art. L162-16-4 of the Social Security Code, available at http://www.legifrance.gouv.fr/affichCodeArticle.do?cidTexte=LEGITEXT000006073189&idArticle=LEGIARTI000025139340&dateTexte=20120814, and Natz et Campion, 2012a.

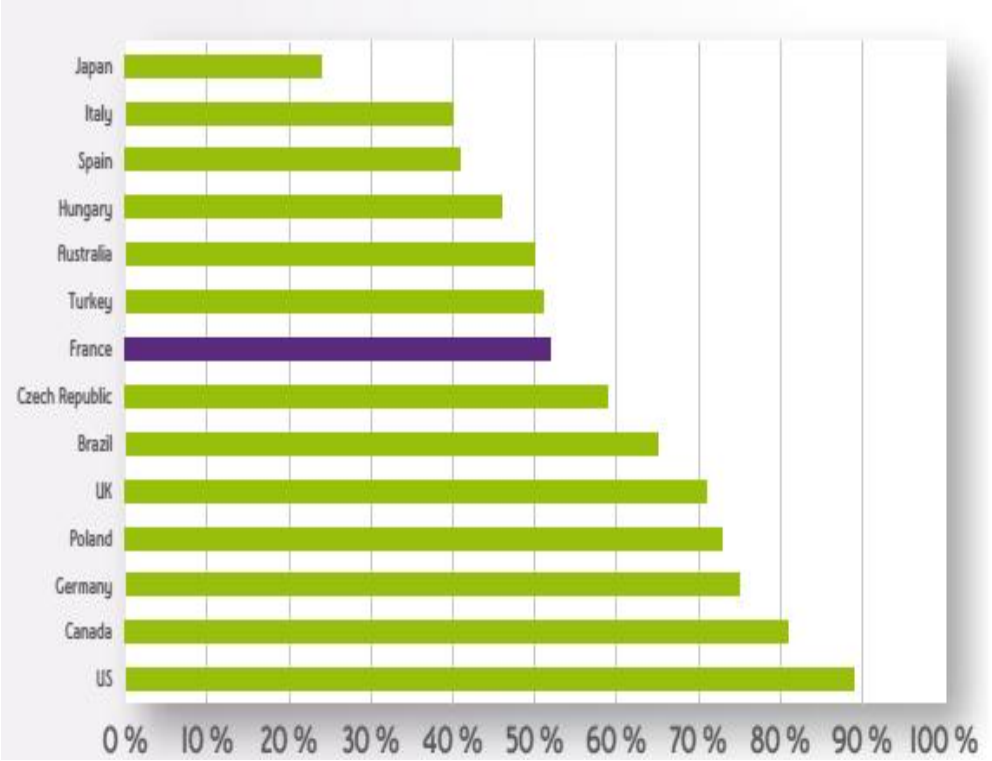
[10] Cf. law n°2002-1487 of 20 December 2002, art. 43 available at http://www.legifrance.gouv.fr/affichTexteArticle.do?idArticle=JORFARTI000001854916&cidTexte=JORFTEXT000000235196, last accessed August 2012.

[11] Data from the website of the mandatory health insurance, www.ameli.fr, last accessed August 2012.

[12] Cf. Social Security Financing Law 1999, available at http://www.assemblee-nationale.fr/budget/plfss1999/sommaire.asp, last accessed August 2012.

Figure 3.3: Market shares of generics among reimbursed medicinal products and international comparisons (in volume in off-patent markets)

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
En quantités	3,4 %	4,4 %	6,0 %	8,0 %	10,6 %	12,5 %	14,9 %	17,5 %	19,5 %	21,7 %	23,6 %	24,3 %	23 %
En valeur	1,8 %	2,2 %	2,9 %	3,9 %	5,1 %	6,4 %	7,4 %	8,3 %	9,3 %	9,4 %	10,5 %	11,4 %	10,9 %



the products are not perfectly substitutable.

A vertical differentiation in the perceived quality between an originator and its generic versions is present in each type of reference pricing scheme. The majority of the models consider the patient as the main actor, taking the decision to consume the off-patent originator or a generic copy. As a consequence, the models assume that the patient is applying their own subjective judgement of the pros and cons of buying a generic version. In the patient's decision, positives include the price of the generic version and negatives, the potential horizontal and vertical differentiation between both versions.

These assumptions and conclusions, as drawn by theoretical papers, will be reviewed according to three aspects: what are the impacts of reference pricing on pharmaceutical expenditure (a), on health outcomes (b), and on the incentives to innovate (c).

a) Impact of reference pricing on expenditure (price and volumes sold)

Zweifel and Crivelli (1996): Prescribing behaviour of physicians and impact on prices

Zweifel and Crivelli's paper (1996) is one of the rare studies which assumes that prescribing doctors make the choice of the medicinal product on behalf of their patients. According to the paper's model, physicians can either prescribe an originator product which is deemed to be of a higher quality without any risk for the patient's health, or a generic version which physicians believe is of a lower quality.

Correspondingly, there are two types of physicians who differ by their risk aversion towards the impact of the quality of the product for their patient's health and have different prescribing behaviours. Those who do not appreciate the difference between the two versions prescribe the cheapest treatment to their patients, whereas those who rate highly the possibility of side effects, continue to prescribe the off-patent originator. In the model assumptions, the off-patent originator, whose patent expired, and generic versions of the product compete "à la Bertrand". Zweifel and Crivelli, by modeling the prescribing behaviour of physicians and the subsequent impact on prices, concluded that the effect on prices depends upon the respective proportion of each type of physician.

As a result, the optimal pricing response of a pharmaceutical company to the introduction of a reference price depends on the prescribing behaviour of physicians. A firm is likely to maintain the price of their product above the reference price when the product is prescribed mainly by risk-adverse physicians, who are only interested in the specific characteristics of the original product and keep prescribing it. If this is not the case, pharmaceutical companies can maximise their profit, by decreasing the price up to the reference price.

Merino-Castello (2003) : Reference pricing leads to a decrease in the price of the off-patent originator Merino-Castello (2003) used a model of vertical differentiation of a duopoly with an originator medicinal product whose patent has expired and a generic version, in order to determine the impact on prices of a reference pricing scheme. She assumed a two-stage game, firstly firms choose the "perceived" quality of the goods they manufacture, and secondly, prices are set by taking into consideration a Bertrand and a Stackelberg price competition. The corresponding decisions on price and quality are respectively analysed in a simultaneous and sequential game framework. Merino-Castello showed that price competition is enhanced by the introduction of a reference pricing scheme. This leads to a decrease in the price of the originator product, while the price of the generic version remains constant. She concluded that both the implementation of the reference pricing scheme and the threat of generic competition lead the manufacturer of the originator product to decrease its price. While price competition is enhanced, the implementation of a risk-sharing scheme does not lead to an increase in the use of generics. In a Bertrand price competition framework, market share percentages remain constant after the introduction of a reference pricing scheme, while in a Stackelberg pricing framework, the market shares of the originator drug may even increase and that of generic versions decrease. The originator manufacturer compensates for the price decrease by increasing the quantities of products sold.

Brekke et al. (2007): Strongest impact of therapeutic reference pricing to drive price down Brekke et al. (2007) introduced in their horizontal and vertical differentiation model the issue of clustering of more or less perfect substitutable products in a therapeutic market consisting of three firms. In this framework, they compared the effects on prices of generic reference pricing and therapeutic reference pricing to the situation without any reference pricing scheme. To this purpose, they assumed that two firms produce an originator product with a different active substance. One of them is still under patent while the other is already off-patent. A third firm manufactures a generic version of the product whose patent has expired, thus both products are in direct price competition. The off-patent originator is considered as safer than the generic version because it has been on the market for a longer period (vertical differentiation). They found that the inclusion in a reference pricing scheme of different therapeutic alternatives (so-called "therapeutic reference pricing") has the strongest impact to drive the prices and profits of the originator down.

Brekke et al. 2011: Endogeneous reference price leads to stronger price competition In a vertical differentiation model, which differs from their model of 2007, Brekke et al. (2011) investigated the impact of a reference pricing by taking into account whether the reference price is set endogenously

or exogenously: the reference price is deemed to be set endogenously when it is a function of the different prices of the products included in the cluster, otherwise it is said to be set exogenously.

Brekke et al. based their model on a policy experiment which took place in Norway in 2003 which replaced price-cap regulation[13] for some off-patent medicinal products. They considered a therapeutic market where two firms are active and manufacture respectively an originator medicinal product whose patent has expired and a generic version. They assumed that patients are heterogeneous in their gross valuation of both treatments, in terms of perceived quality difference, which might for example be due to advertising expenses. As a copayment rate and a reference price are implemented, patients make concessions in their decisions, such as drug quality compared with the out-of-pocket payment. Brekke et al. analysed the patient decisions by considering alternatively an exogenous and an endogenous reference price.

Brekke et al. found that a reference price reduced both brand-name and generic prices, and resulted in lower brand-name market shares. They also found that a scheme with a reference price set endogenously leads to more price competition than when the reference price is set exogenously. They explained their result by the fact that an endogenous reference price means that the frequency of the update of the reference price has an impact on the pricing strategy. Consequently, the more frequent the reference price is updated, the stronger is the price decrease in the reference price cluster. By analysing a panel data set of off-medicinal products from 2001 to 2005, they found on average that the introduction of a reference pricing scheme led to a decrease of the market shares of originator products by 15% due to a shift of demand towards the generic version, even if the price of the off-patent originator decreased.

As a general conclusion from the different models reviewed, results depend highly upon the specific features of the reference pricing system in place. However, all models concluded that reference pricing more or less drives the prices of originators as well as the profits of originator and generic companies down. However, the impact on the prices of generics is more subtle.

b) Impact of reference pricing on health outcomes

Brekke et al. (2007): Higher risks for patients health with generic reference pricing
Brekke et al. (2007) also investigated in their model the impact of a reference pricing scheme on the health outcomes of patients. By comparing different types of reference pricing scheme, "therapeutic reference pricing" (clustering on a therapeutic basis) and "generic reference pricing" (clustering on the molecule basis), they found that including only generic versions of a drug in the cluster distorts drugs

[13] Price-cap regulation corresponds to a maximum price that the firm is allowed to charge.

choices most when compared to a therapeutic reference pricing. Consequently, they found that when the cluster only includes generics, meaning products with the same active ingredient, patients are exposed to higher risks for their health.

c) Impact of reference pricing on innovation incentives

Brekke et al. 2007 Brekke et al. (2007) found that a reference pricing system increases price competition, and decreases prices and profits which leads to a decrease in incentives for firms to innovate. This result is in line with the results of Danzon (2001) who in her paper stressed that a reference pricing scheme drives prices down, and at the same time decreases the incentives of firms to invest in R&D.

Bardey et al. 2011: Impact of reference pricing on the intensity of R&D Finally, Bardey et al. (2011) in a model with vertical and horizontal differentiation involving innovative firms, health regulators and patients/physicians evaluated the long-term impact of the introduction of a reference pricing scheme on innovation, health conditions of patients and government expenditure. In their model which is based on the French healthcare system of a statutory health insurance and regulated prices, Bardey et al. considered that physicians's and patients's incentives are perfectly aligned, resulting in an ideal physician-patient relationship.

Bardey et al. found that a reference pricing system negatively affects the intensity of research and delays the introduction of new drugs. It decreases the intensity of research because it deters small innovation (so-called "follow-on innovation") which would fall under the reference pricing scheme, whereas for highly innovative drugs (so-called "pioneer drugs"), it will have no effect.

As a general conclusion of the different models, a reference pricing scheme is often criticised for its negative impacts on innovation incentives. Its effects depend mainly on its general features with respect to the size of the cluster and the frequency of the update of the reference price. The costs in terms of administrative work are rarely taken into account in the various models.

General conclusion on the impact of reference pricing Lopez-Casasnovas et al. (2000) performed a review on the papers dedicated to reference-pricing. They found that the reference pricing scheme's features are important in determining the effects on innovation. Thus, the inclusion of on-patent drugs in the scheme creates an erosion of the patent rights. Firms hence have fewer financial incentives to develop new indications or to innovate incrementally (so-called "follow-up drugs" or "me-toos drugs") as these innovations would fall in a reference price group. Even if on-patent drugs are excluded, they show that a reference pricing scheme has a negative impact on innovation. This is due to the uncertainty created by a

reference pricing scheme concerning the expected returns on investment, because some schemes developed an incomplete exclusion of on-patent medicines. This may be the case for products with a process patent, a patented new galenic form or with a patent for a further developed indication.

The ESMT study (2009) focusing on price regulation and incentives to innovate shows that all forms of price regulation reduce the value of projects. By decreasing prices, it also reduces the resources available for R&D. With regard to reference pricing schemes in particular, it notes that projects in early development phases are affected when on-patent drugs are included in the scheme. R&D investment by firms is de facto directed towards indications with a lower probability for the drug to end up being "late in class" and falling into the reference pricing scheme. Consequently, firms target their research towards products in therapeutic indications affecting a smaller number of patients such as rare diseases or projects with a lower probability of success. The ESMT study concludes that it is important for the reference price to be set at an effective level, otherwise distortions may be created or enhanced.

3.1.4.2 Empirical literature on reference pricing

Empirical impact on prices and market shares The empirical literature around internal reference pricing focuses mostly on its impact on the market shares of originators, prices and public expenditure.

Giuliani et al. (1998) studied the impact of the implementation of the reference pricing scheme in Germany on drugs costs from 1990 to 1996. They observed that the prices of therapeutic substitutes included in the reference pricing scheme decreased during this period while the spending on medicines outside the scope of the reference pricing scheme increased.

On the topic of market shares of originators, Aronsson et al. (2001) and Bergman et al. (2003) investigated the effect of the introduction of a reference pricing system on the market shares of originators using data from Sweden, from 1972 to 1996, and found negative effects as the market shares of the originators decreased in the period during which a reference pricing system was implemented from 1993 onwards.

Concerning the impact on the price of off-patent originators and generic versions, Pavcnik (2002) investigated the impact of the introduction of a reference pricing scheme in Germany in 1989 by using data from the oral antidiabetics and antiulcerants markets between 1986 and 1996. He found for oral antidiabetics, that prices decreased on average by 18%, respectively 11% for generics and 28% for originators following the introduction of a reference pricing scheme. By taking data from medicines in Spain after the implementation of a reference pricing scheme in 2000, Puig-Junoy (2003) found that a reference price acts as a ceiling price, i.e. that no product will be priced lower than the reference price set.

Combe and Haug (2006b) investigate the impact of the TFR in France which consists of reimbursing

the products on the basis of the price of generics, for ninety molecules in forty-four different therapeutic classes from February 2001 to January 2006. They found that in the short-term, a reference pricing scheme has a positive effect, but a negative effect in the long-term due to the lack of incentives given to pharmacists to deliver cheap generic versions. Due to the specific structure of the TFR, they found that reference pricing favours the development of generics which are not included in the reference price clusters.

Brekke et al (2009) investigated the effect of the implementation of a reference pricing scheme in Norway in 2003 by using data from 2001 to 2004. By comparing the effects of different measures such as reference pricing and price cap regulation, they found that a reference pricing scheme has the strongest effects in decreasing pharmaceutical prices. Specifically, the decrease is more pronounced for originators (around 19%) than for generic products (around 8%).

In a more recent paper, Brekke et al. (2011) investigated in a vertical differentiation model the impact of reference pricing on the competition between brand name and generic products on the prices and market shares of both products. In order to assess the impact of the introduction of a reference price on pharmaceutical expenditure, Brekke et al. took as a proxy the average price of the molecules (meaning the prices of the originator product and of the generic version weighted by their respective market shares). They found an overall decrease of the average molecule price by 30% due to the decrease of prices for the off-patent originator product and a shift of demand towards lower-priced generics.

These empirical results have to be interpreted with care as it is important to control for other cost-containment measures.

Empirical impact on patients' health Patients' health, was the focus of Grootendorst et al. (2002) investigation on the effect of the introduction of a reference pricing scheme in three different markets in British Columbia, nitrates, ACE inhibitors, and Calcium Channel Blockers (so-called "CCB") on the health status of patients over 65 years. They found that a reference pricing scheme enables a yearly saving of around $7.7 million between 1995 and 1999 without any increase of the morbidity and mortality rate. However, the number of consultations by physicians increased during this period due to the patient's need for information on alternative treatments. Grootendorst et al. found that the consultation for ACE inhibitors increased by 15% in the fifteen months after the introduction of the reference pricing scheme.

Stargadt (2010) investigated the impact of the inclusion of the category of statins in the reference pricing scheme in Germany on January 2005 with regard to pricing and prescribing behaviour. Statins are widely used to lower cholesterol levels and have an important impact on public health expenditure. Stardgadt's analysis focused on atorvastatin which belongs to the class of statins - claimed by its manufac-

turer - to be superior to other statin drugs due to its reduced side-effects and its drug interaction profile. Atorvastatin was however classified by the competent authority in Germany as a me-too drug and was included in the reference pricing scheme. The price of atorvastatin, however, was not decreased by the manufacturer, thus patients treated with atorvastatin had to pay, in addition to the usual copayment, the difference between the copayment price and the retail price. Stargadt showed that the market shares of atorvastatin decreased from 33.2% in January 2005, to 4.8% in 2006. The volume of other lipid-lowering drugs remained constant. Having reviewed the different models, some criticism can be raised as most models place too much emphasise on the role played by the patient in the consumption decision and the vertical product differentiation between originator and generic.

3.1.4.3 Criticisms of the different theoretic models

The role of the prescribing physician With the exception of Zweifel and Crivelli (1998) and Bardey et al. (2011), all of the models consider patients as the decision-makers in their choice of medicinal product. However, with the exception of the OTC segment, medicinal products can only be bought on-prescription at the pharmacy. By neglecting the prescription physician, the models missed the physician agency dimension which exists between the physician and the patient. The physician is the one making the decision about the medicinal product and writing the prescription. The extent to which the physician takes into account the patient´s utility might vary amongst physicians.

Bardey et al., by assuming a perfect patient-physician relationship also missed issues relating to information imperfections and agency relations which are at the heart of the implementation of reference pricing schemes, in particular due to the presence of the off-patent originator which is in direct competition with generic versions.

Excessive role of the vertical product differentiation While horizontal differentiation among therapeutic classes is relevant in the case of a reference pricing scheme due to the different active ingredients, modes of action, and side-effects that exist, in particular in case of therapeutic reference pricing, vertical differentiation based on quality perception from the point of view of the consumer is not relevant.

Generics have been approved by health regulatory authorities and are bioequivalent to the off-patent originator. The same active ingredients are shared by originator and the generic versions and also the same leaflet. They may simply differ only in the main excipients or inactive ingredients which may affect patient at the margins, for example in the case of an allergy to one excipient. The literature, however focuses on these differentiation patterns from the patient´s point of view.

Vertical differentiation from the prescriber´s point of view may be more relevant as it can influence

prescribing behaviour. While the originator and the generic versions are bioequivalent, the physician may have more information on the originator or be used to prescribing it. Thus, this vertical differentiation should be taken into account. The models reviewed missed this aspect which is also at the heart of the implementation of a reference pricing.

Based on the criticisms expressed, the next section will focus on modeling the functioning of a reference price system by taking into account the existing information advantage in favour of the off-patent originator.

3.2 Modeling the functioning of reference pricing with information advantage

After a brief description of the aim of the following model to show how a reference price system can contribute to alleviate the effect of the existing information advantage in favour of the originator (3.2.1), the framework and the assumptions are described (3.2.2) and a reference price introduced (3.2.3). The last subsection concludes on the results found (3.2.4).

3.2.1 Aim

Motivation and method The different models reviewed showed that the implementation of a reference pricing scheme aims at aligning the prices of originators with those of the generic versions and at promoting the use of generics by increasing the elasticity of demand above the reference price set. The demand for medicines is defined by physicians acting as agents for their patients and is influenced by their prescription patterns and the information they have on products.

The objective, therefore, is hence to analyse according to a basic framework the impact of advertising activities by originator manufacturers on the demand for originator and generic products, on prices and profits in a vertical differentiation model which considers physicians as responsible for taking the final consumption decision. Königbauer (2007) analyses the impact of persuasive advertising on generic market entry and on social welfare. She finds that advertising by an originator firm increases the perceived quality of the product by the prescribing physician.

Consequently, it should be observed how the implementation of a reference pricing system, by increasing the elasticity of demand, can alleviate the impact of the information advantage experienced by the originator. As a basis, Königbauer's model (2007), where the physician's prescription decision is analysed in the presence of a heavily advertised originator and a generic, will be taken and extended in order to introduce a reference pricing scheme and therefore conclude on its impacts on the demand for generics, prices and profits.

3.2.2 Framework and assumptions of the model

Framework of the analysis As in the framework set by Königbauer (2007), this analysis focuses on a market for prescription drugs consisting of a continuum of patients distributed uniformly within the segment $[0;\bar{t}]$. The patients' position on $[0;\bar{t}]$ can be interpreted as the extent to which they are ill and corresponds to their valuation for the treatment: $v(t) = t$. Hence, the more severely patients are ill, the

higher their willingness to pay. For the sake of simplicity, $\bar{t}$ is normalized to 1.

Consider also that all patients suffer from the same condition and can be treated by an originator product (B) or a generic version (G) which are both available on-prescription only.

Utility of the patient Königbauer defines the utility of a patient located at t as $u_{i,t} = t - p_i$ with $i = G, B$, meaning that utility of patients is equal to their valuation for the treatment minus the price of this treatment, p_i. The off-patent originator and the generic version are assumed to have the same quality, due to the fact that the generic version has demonstrated to health authorities its bioequivalence to the off-patent originator during the marketing authorisation approval phase. Due to both products' identical ability to treat the disease, patients value the originator and the generic version equally when their treatment is prescribed.

In addition to Königbauer's model, the variable θ is added representing physicians' price sensitivity, where a term a avoids that the utility becomes negative, so that $u_{i,t} = a + t - \theta \cdot p_i$. Patients never bear the full price of the medicines but only a certain part of the costs which the physicians take into account in their prescription decision.

Utility of the physician Assuming, as in Königbauer's framework, that there is a mass normalised to 1 of ex-ante identical physicians who can choose to prescribe either the originator or the generic version. It may be supposed, as physicians act in an agency relation on behalf of their patients, that they also take into account the valuation of the treatment for their patients and substract the price the patients have to pay (Mc Guire, 2000).

Agency relation physician-patient Physicians have a central role in the following model as they are the agent of their patients. Patients go to their physicians to solve uncertainty issues regarding their health status. They expect physicians to make the appropriate decision on their behalf as they are deemed to have a superior medical knowledge. Consequently, physicians are believed to be faithful agents for their patients and for society. Physicians know the value the patient places in the different health outcomes. The physician agency results from the interaction between the information advantage of the physician and the market power which is created (Chalkley et al. 2005).

Stern et al. (1981) described the physician's act of prescribing as the function of "matching" patients with a drug. This matching depends on the physician's diagnostic skills and on the investment each physician makes in learning about each individual drug. Stern et al. investigated a sample of 1500 prescriptions in the treatment of depression and hypertension in the US. They found that, while prescription patterns differ among physicians, the characteristics of the drug also impact the prescription decision.

Interestingly, they found that physicians who prescribe in a "concentrated" way (meaning who do not prescribe a diversified portfolio of medicinal products) tend to prescribe originators having high market shares and advertising expenses.

Persuasive advertising Based on these empirical studies, it may be assumed in this model that physicians were the target of persuasive advertising by the firm manufacturing the originator during the period when it was patent-protected and the only treatment on the market. It may also be assumed that these advertising expenses lead to a distortion in the choice of prescription in favour of the originator as it creates an information advantage in the form of a perceived quality differentiation with the generic version, when it becomes available following the expiry of the patent.

Hence, the physicians' valuation for the originator increases from t to ct with $c > 1$ due to the information advantage in favour of the originator. This results in a vertical product differentiation as physicians, as a result of these advertising expenses, overestimate the quality of the off-patent originator compared to the generic. The term c represents the prescription habit of physicians who are used, from the time the originator product was the only one available, to prescribe it (Hellerstein, 1998). Consequently, out of habit and due to the fact that they are more informed about the efficacy of this drug, they are more likely to prescribe the off-patent originator. Thus, it possesses an advantage as it was the first on the market and has been advertised and marketed for a long time in comparison with the generic version.

Assuming that each patient needs one version of the drug, the utility of the physician can hence be written:

$$U_{i,t} = \begin{cases} a + t - \theta \cdot P_G & if \quad i = G \\ a + c \cdot t - \theta \cdot P_B & if \quad i = B \end{cases}$$

The physician's prescription choice In this vertical differentiation configuration, the originator is prescribed when $a + ct - \theta \cdot P_B > a + t - \theta \cdot P_G$ meaning for high valuation patients with a valuation t such as, $t > \hat{t} = \frac{\theta \cdot (P_B - P_G)}{(c-1)}$. Patients who have a valuation $t < \hat{t}$ are prescribed the generic version.

It may be assumed for the derivation of the demand that the mass of prescriptions of the originator product is equal to $(1 - \hat{t})$.

Derivation of the demand Starting from the prescription behaviour of physicians, the demand for generics D_G can be defined as

$$D_G = \begin{cases} 1 \; if \; \hat{t} > 1 \iff P_B - P_G > \frac{(c-1)}{\theta} \\ \frac{\theta(P_B - P_G)}{(c-1)} \; if \; 0 < \hat{t} < 1 \iff 0 < P_B - P_G < \frac{(c-1)}{\theta} \\ 0 \; if \; \hat{t} < 0 \iff P_B < P_G \end{cases}$$

and the demand for originator D_B as

$$D_B = \begin{cases} 1 \; if \; \hat{t} < 0 \iff P_B < P_G \\ 1 - \frac{\theta(P_B - P_G)}{(c-1)} \; if \; 0 < \hat{t} < 1 \iff 0 < P_B - P_G < \frac{(c-1)}{\theta} \\ 0 \; if \; \hat{t} > 1 \iff P_B - P_G > \frac{(c-1)}{\theta} \end{cases}$$

Equilibrium prices and profits Therefore, firms choose their prices by taking the quantities sold as fixed and maximise their profits in respect to prices, which leads to the equilibrium prices.

In light of Königbauer, it may be postulated that the advertising level has been chosen in a previous period, and the fixed costs of generic entry are already sunk so that these costs are irrelevant in the optimisation problem. The production costs are also normalised to zero for simplification purposes.

Thus, the profits of the generic and originator firm, may be calculated as follows:

The profits of the generic firm can be written as:

$$\Pi_G = P_G \cdot D_G = \begin{cases} P_G & if \; P_B - P_G > \frac{(c-1)}{\theta} \\ P_G \cdot \frac{\theta(P_B - P_G)}{(c-1)} & if \; 0 < P_B - P_G < \frac{(c-1)}{\theta} \\ 0 & if \; P_B < P_G \end{cases}$$

and the profits of the originator firm as:

$$\Pi_B = P_B \cdot D_B = \begin{cases} P_B & if \; P_B < P_G \\ P_B \cdot (1 - \frac{\theta(P_B - P_G)}{(c-1)}) & if \; 0 < P_B - P_G < \frac{(c-1)}{\theta} \\ 0 & if \; P_B - P_G > \frac{(c-1)}{\theta} \end{cases}$$

By deriving the profits, equilibrium prices may be ascertained:

$\frac{\partial \Pi_G}{\partial P_G} = \frac{\theta(P_B - P_G)}{(c-1)} - \frac{\theta P_G}{(c-1)} = \frac{\theta(P_B - 2P_G)}{(c-1)} \stackrel{!}{=} 0 \iff \theta(P_B - 2P_G) = 0 \iff P_G = \frac{1}{2} P_B$

$\frac{\partial \Pi_B}{\partial P_B} = 1 - \frac{\theta(P_B - P_G)}{(c-1)} - \frac{P_B \theta}{(c-1)} = 1 - \frac{\theta(2P_B - P_G)}{(c-1)} \stackrel{!}{=} 0 \iff P_B = \frac{1}{2} \cdot (\frac{(c-1)}{\theta} + P_G)$

By replacing with $P_B = 2P_G$, the outcome is $P_B = \frac{2(c-1)}{3\theta}$ and $P_G = \frac{(c-1)}{3\theta}$ can be written. Prices of both off-patent originator and generic are increasing in c. Consequently, P_B is equal to twice P_G.

In the same way, by replacing the equilibrium prices P_B and P_G, the profits of the originator and generic products may be determined as $\Pi_G = D_G \cdot P_G = \frac{1}{3} \cdot \frac{(c-1)}{3\theta} = \frac{(c-1)}{9\theta}$ and $\Pi_B = D_B \cdot P_B = \frac{2}{3} \cdot \frac{2(c-1)}{3\theta} = \frac{4(c-1)}{9\theta}$.

As the respective utilities must be positive, corresponding to $a + t - \frac{(c-1)}{3\theta}\theta \geq 0$ and $a + ct - \theta\frac{2(c-1)}{3\theta} \geq 0$, by setting a at least equal to $\frac{2}{3}(c-1)$ ensures this.

Results are summarised in the table 3.2.

Table 3.2: Comparative table

	Price	Profits
Originator product	$P_B = \frac{2t(c-1)}{3\theta}$	$\Pi_B = \frac{4t(c-1)}{9\theta}$
Generic version	$P_G = \frac{t(c-1)}{3\theta}$.	$\Pi_G = \frac{t(c-1)}{9\theta}$

Conclusion on the impact of advertising Information advantage distorts the physician's evaluation of the medicines and their prescription choice in favour of the originator by a term c. This term c impacts the prices, the demand and the profits of the off-patent originator and the generic version.

3.2.3 Introduction of a reference pricing scheme

A reference pricing system may now be introduced into this basic framework, meaning an additional optional copayment that patients have to pay out-of-pocket when the price of the product is above the reference price set. By linking the optional additional copayment to the price of the medicinal product, this policy measure aims to increase the price elasticity of demand. Therefore, it is of interest to investigate the extent to which a reference pricing scheme impacts the prices and profits of the generic and the originator, and can decrease the information advantage which favours originators.

Assumptions For the purpose of simplicity, the reference price is set as (P_{RP}), to be equal to the price of the generic version, $P_{RP} = P_G$. This assumption is in line with the empirical setting of reference prices in the different EU member states, where the reference price is set as a general rule around the average price of the generic versions. This reference price corresponds to the maximum price reimbursed. Patients have to pay the full difference between the reference price and the price of the product, if the price of the product is above the reference price.

Utility of the patient and the physician's prescription choice under the reference pricing system As the utility of patients changes due to the presence of a reference price, the utility of physicians also evolves as they take into account the utility of their patients. Their new utility function can be written as:

$$U^*_{t,i} = \begin{cases} a + c \cdot t - (P_B - P_G) - \theta \cdot P_G & if\, i = B \\ a + t - \theta \cdot P_G & if\, i = G \end{cases}$$

Hence the physician prescribes the originator when $ct - P_B + P_G(1-\theta) > t - \theta \cdot P_G$ meaning for all patients with $t > \tilde{t} = \frac{(P_B - P_G)}{(c-1)}$ and the generic version for the rest of the patients, with $t < \tilde{t}$.

The comparison of the value of $\hat{t}$ and $\widetilde{t}$ in the presence or not of a reference price shows, as $\theta \in [0;1]$, that $\tilde{t} \geq \hat{t}$.

Equilibrium prices and profits As $\tilde{t} = \hat{t}$ when $\theta = 1$, the optimisation problem of both firms is analog to the case analysed previously. The optimal prices are equal to $P_B = \frac{2(c-1)}{3}$ and $P_G = \frac{(c-1)}{3}$. In both cases, the prices of both products are increasing in c, meaning that the greater the information advantage, the higher the rate of prescription of the originator by the physician. As in the framework without a reference pricing scheme, the price of the originator product is always twice as much as the price of the generic version.

The respective profits of the originator and the generic version are equal to $\Pi_G^* = \frac{1}{9} \cdot (c-1)$ and $\Pi_B^* = \frac{4}{9} \cdot (c-1)$.

As previously, the respective utilities must be positive, corresponding to $a + t - \frac{(c-1)}{3\theta}\theta \geq 0$ and $a + ct - \theta\frac{2(c-1)}{3\theta} \geq 0$, by setting a at least equal to $\frac{2}{3}(c-1)$ ensures this.

With the introduction of a reference pricing scheme, the variable which represents the physician's price sensitivity θ, $\theta < 1$, disappears from the profit and the price function so that equilibrium prices of both the generic and the originator version decreased by θ.

3.2.4 Results

Calculation of the demand price elasticity Reference pricing is supposed to lead to an increase of the elasticity of demand above the reference price. Now, calculating the price elasticity with and without the implementation of a reference pricing scheme for the off-patent originator product is considered in order to determine to which extent the price elasticity ε_B increases after the implementation of a reference pricing scheme.

When $P_B - P_G < \frac{(c-1)}{\theta}$, the price elasticity of demand for the off-patent originator product can be written as: $\varepsilon_B = \frac{\theta}{(c-1)} \cdot \frac{P_B}{D_B} = \frac{\theta}{(c-1)} \cdot \frac{P_B}{1-\frac{\theta(P_B-P_G)}{(c-1)}} = \frac{\theta P_B}{(c-1)-\theta(P_B-P_G)}$.

By calculating the price elasticity for the originator after the implementation of the reference pricing scheme when $P_B - P_G < (c-1)$, it is now equal to

$\varepsilon_{BRP} = \frac{1}{(c-1)} \cdot \frac{P_B}{1-\frac{(P_B-P_G)}{(c-1)}} = \frac{P_B}{(c-1)-(P_B-P_G)}$.

By comparing both expressions, as $P_B > P_G$, $\theta \in [0;1]$ and $c > 1$, then $\varepsilon_B < \varepsilon_{BRP}$. Hence, as predicted, the price elasticity of demand for the originator product increased with the implementation of a reference pricing scheme, while the distortion brought by the physician's price sensitivity θ disappears. The distortion brought by c remains, even with the implementation of a reference price, which leads to a weakening of the information imperfection.

Conclusion The comparison of prices and profits with and without a reference price leads to the conclusion that the reference price eliminates the effect of physician's price sensitivity which counterbalances the effects of the information advantage in favour of the originator. As a consequence, the prices and profits of the originator decrease in the presence of a reference pricing scheme. The model showed that the price elasticity of demand for originators also increases following the implementation of a reference pricing scheme. Additionally to Königbauer's results, the model, by introducing a reference price, leads to the conclusion that a reference pricing scheme weakens the originator's existing information advantage, by suppressing the term θ. However, it does not make the term c disappear.

The results of the model depend upon the assumptions made, especially with regards to the physician's prescription behaviour in terms of internalisation of the utility of their patients and the extent to which the advertising of an originator distorts the physicians' prescription choice.

Policy implications The model shows that the effects of the information advantage favouring off-patent originators still remain with the introduction of a reference pricing scheme. The distortion towards higher-price products, brought about by the presence of health insurers acting as the final payers, decreases by setting a reference price which eliminates the effect of the physician's price sensitivity.

Reference pricing scheme and complementary measures Therefore, in order to reinforce the effect of a reference pricing scheme and further decrease the information advantage of the off-patent originator, other measures are needed. These measures can be implemented either at the physician level, with for example, the use of INN prescription, and at the pharmacist level with, for example, the mandatory generic substitution, which is widely implemented in member states in order to foster the demand for generics. Through the use of mandatory INN prescriptions, physicians are obliged, for molecules which are genericised, to prescribe by using the name of the active ingredient and not by mentioning the name of one brand of the product. The pharmacist will therefore offer the patient a cheaper product. Some countries actively recommend the use of INN prescribing which empowers physicians and pharmacists in their choice of the adequate treatment. The choice of product will highly be a function of the therapeutic margins of the drugs available and the specifics of the patient, in terms of factors such as age, condition etc. Measures can also be taken at the pharmacists' level to give them incentives, or oblige them to deliver the generic version of an originator product. For example, mandatory generic substitution obliges pharmacists to deliver the generic version of the product to the patient, when physicians prescribe an originator which is more expensive than its generic equivalent. Generic substitution does not apply when a physician explicitly mentions on the prescription that substitution is forbidden. In Germany, for

example, the mandatory generic substitution obligation is strengthened by the existence of agreements between health insurance funds and pharmaceutical manufacturers of rebate contracts[14]. In cases where a rebate contract was signed between the pharmacy and the health insurer, the pharmacy is only allowed to substitute for the product the patient's health insurance funds signed a rebate contract with. Both measures described are widely implemented in the EU and are complementary to the introduction of a reference pricing scheme to further decrease the information advantage.

This second section showed that the introduction of a reference pricing scheme increases the elasticity of demand above the reference price set. A reference price serves to eliminate the distortion of the physician's price sensitivity. Thus, it counterbalances the effect of the information advantage experienced by off-patent originators.

While reference pricing schemes are implemented by governments as a cost-containment measure in off-patent markets, it impacts on-patents markets and pharmaceutical firm's incentives to innovate. A product which is not acknowledged as innovative might fall under the reference price system, as is the case in Germany. It may now be shown that by clustering substitute products and setting a reference price, the implementation of a reference price impacts the pharmaceutical companies' incentives to innovate. By grouping follow-on products with generic versions based on their therapeutic substitutability and setting a reference price, it may be ascertained how reference pricing might redirect the pharmaceutical companies' investment expenses towards high-value innovative products.

[14]For more details, cf. par. 130 a of the German Social Law Code ("Sozialgesetzbuch V"), available at http://www.sozialgesetzbuch.de/gesetze/05/index.php?norm_ID=0513000.

3.3 Modeling the impact of reference pricing on innovation incentives

Once the benchmark model and the underlying conclusions of Ganuza et al. (2007, 2009) and its extensions have been reviewed (3.3.1), the impact of a reference pricing scheme on the pharmaceutical companies' incentives to innovate follows, which is analysed based on a model adapted from Königbauer and Ganuza et al. (3.3.2).

3.3.1 Review of the benchmark model of Ganuza et al. (2007, 2009)

Firstly, the framework proposed by Ganuza and the related assumptions are described (3.3.1.1) and the results presented (3.3.1.2). Finally, the extensions proposed by Ganuza are briefly analysed (3.3.1.3).

3.3.1.1 Framework and assumptions

Motivation The following model is based on the settings of Ganuza et al. (2009) who proposed a model where the low price elasticity of demand explains the presence of a bias towards small innovation improvements by pharmaceutical firms.

By small improvements, Ganuza et al. mean the trend whereby firms focus on small improvements within a product, so-called me-too drugs or follow-on drugs, as opposed to new molecular entities (hereinafter NMEs). They explained this trend by the fact that firms experienced a greater reward from smaller improvements, targeted at the low price elastic segment of demand than from bigger improvements which target the whole population. Their reasoning is in line with the empirical results of the Sector Inquiry (DG COMP, 2009) which offers a separation between incremental innovation and follow-on products.

The model proposed by Ganuza et al. is of particular interest as it does not follow the mainstream literature which explains the underinvestment in R&D and innovation by the lack of internalisation of the surplus of innovation generated[15] (Nordhaus, 1969). Nordhaus, who investigated the field of patent length, explained that a fundamental trade-off exists between static and dynamic considerations in designing patent policy. Giving firms incentives to innovate happens at the expense of competition. Nordhaus concludes that long-life patents increase firms' incentives to innovate and are desirable when the R&D costs and/or price elasticity of demand are high.

Contrary to Nordhaus, Ganuza et al. (2007, 2009) argue that a firm's choice on their level of innovation will depend on how close the pharmaceutical company's private profits are to the social value afforded by

[15] Nordhaus W., Invention, Growth and Welfare: A Theoretical Treatment of Technological Change, Cambridge Mass., 1969, MIT Press.

this innovation. With small innovations, firms appropriate a higher surplus than the social contribution generated by their innovation which incites them to invest in less innovative projects. Thus, a bias towards small innovation appears due to the low price sensitivity of demand in pharmaceutical markets caused by the presence of health insurers, who are the final payers, and by the marketing expenses aimed at increasing brand loyalty. Thus, they show that a reference pricing scheme which increases the price elasticity of demand can partly remedy this bias towards small innovations.

Framework and assumptions Ganuza et al. in their basic benchmark model considered a market where a number of firms produce a prescription drug. One of the firms can invest in R&D to increase the quality of its product. It is assumed that the quality improvement depends on the level of the R&D effort undertaken by the firm. The greater the effort, the higher the probability of having a high-quality product.

The demand in the model of Ganuza et al. corresponds to a unit mass of patients who are price inelastic, as the costs are fully borne by a health insurance. As medicines can only be bought on prescription, the demand for drugs corresponds to the physicians' prescription choice.

Ganuza et al. assume that prescribing physicians are heterogeneous in their preferences and are consequently more or less price elastic. They assumed that a certain proportion of physicians fully internalise their patients' preferences and prescribe the highest-quality product regardless of the price. These physicians are characterised by Ganuza et al. as "captured physicians" as their preferences are identical to that of their patients. The rest of the physicians integrate the benefit of the drug for their patients, as well as the product's price in their prescription choice. They are refered to by Ganuza et al. as the "non-captured doctors". As for the timing, during an initial stage, firms choose the innovation efforts, which is then realised in the second stage and leads to the equilibrium prices.

3.3.1.2 Results

Market equilibrium: First best and second best Ganuza et al. derive the optimal allocation of the goods from a social point of view by assuming that all patients are alike and consume the product with the same given quality.

The firm's decision regarding the effort employed for innovation in the first stage depends on profits. Even if the patient does not bear the full costs of the drug, the price plays a role as the non-captured physicians integrate the price of the product in their utility function and prescribe the product only if it provides them with a positive utility. The firm will maximise its profits by setting a different price whether it intends to sell the drug only to the captured doctors who are price inelastic, or to all physicians.

Consequently, depending on the market segment targeted, prices and profits differ.

Ganuza et al. show that when the proportion of captured physicians is equal to 0, the private choice of effort coincides with the first best solution. However, when the proportion of captured physicians differs from zero, distortions arise because firms appropriate a higher surplus than the social value of their innovation. The model predicts, by comparing the optimal decision effort and the decision effort of the firm i, that a bias exists towards small improvements in the firm's decision effort when the proportion of captured physicians is positive.

For high-quality products, Ganuza et al. found that the firm maximises its profits by setting a lower price and targeting the whole market while for low improvements, it maximises its profits by setting a higher price and selling only to inelastic physicians. Ganuza et al. concluded that larger innovations are associated with higher profits but do not necessarily lead to higher prices.

Solving the bias towards small improvements Ganuza et al. showed that solutions to this bias consist of decreasing the reimbursement level by introducing either a copayment or a reference price.

Copayments consist of a fixed percentage of the price to be paid by the patient, or a fixed amount regardless of the price, and result in the decrease of the excessive rents stemming from small innovations, as the captured physicians become more price sensitive. Copayments increase the firms' incentives to invest in R&D. However, for low quality products, Ganuza et al. found that the profits of the firms still exceeded the social value of their innovation.

Another way to alleviate the bias is to introduce a reference pricing scheme. The implementation of a reference price increases the price elasticity of demand and aligns health agencies' own goals with the incentives of patients and prescribing physicians. Ganuza et al. show that setting a reference price equal to 0, meaning that the full costs are borne by the patients, leads to a full convergence of the incentives of health insurers and firms so that the first best solution is achieved.

3.3.1.3 Extensions of the benchmark model and criticisms

Extensions of the benchmark model Ganuza et al. (2007) noted that the low price sensitivity of demand triggered by health insurance can be reinforced by a firm's specific behaviour, such as advertising. Consequently, putting aside the assumption of the existence of captured doctors due to exogenous preferences, they explain doctors' behaviour by the firms' marketing efforts, which can be either persuasive or informative.

In an extension of their benchmark model, Ganuza et al. explained why a firm chooses persuasive or informative advertising and what the impact is of these choices on physicians' prescription behaviour.

In their assumptions, the firm can choose to send physicians informative or persuasive advertising. Persuasive advertising is characterised as transmitting a "noisy" estimation of the quality of the product. Persuasive marketing leads to a distorted demand and contributes in a reduction of demand elasticity.

On the other hand, the firm can choose to spend money for informative advertising which is deemed to elicit the real value of the product. Informative advertising, therefore, has no impact on the utility function which remains the same as without advertising.

Ganuza et al. showed that a firm chooses persuasive advertising when the quality improvement of its product is low and informative advertising when the quality improvement is high. They concluded that R&D and marketing can be considered as some kind of substitute strategy by pharmaceutical firms.

Criticisms on the model of Ganuza et al. (2007, 2009)

Assumptions concerning physicians' prescription behaviour The model's conclusions are very dependent on the assumptions made over the physician's prescription behaviour. Hence, why do some physicians take the real costs of the medicines into account and others not at all?

With the different cost-containment measures implemented at national level and the presence of out-of-pocket payments for the patient, it seems highly unlikely that a physician would not take into account the price without an additional incentive. Physicians are given financial and non-financial incentives to offer price-effective prescriptions.

It does however make sense to suppose that behaviour differs amongst physicians, meaning that some physicians take the full cost of the product for health insurance into account, while others only take into account the price paid by the patient. Physicians are the agents of patients, thus they internalise the utility of their patient in their prescription choice. The extent of the internalisation, however, may differ among physicians. Physician agency issues also arise also from the physician's information advantage over the patient (Mc Guire, 2000). Once a diagnosis has been made, doctors should decide which drug to prescribe. The extent to which they take into account economic considerations is unclear. The economic considerations of patients play a role in the therapeutic choice of the physician (Gonül et al., 2001). The full internalisation of the patients' price incentives and of the insurer's costs consequently represents interesting extreme cases (Kina, 2008).

Assumptions concerning advertising Ganuza et al. (2007) introduced the issue of advertising in the extension of their benchmark model. While they consider that informative advertising elicits the real value of the product, they define persuasive advertising as transmitting a noise which leads to a decrease in the demand elasticity.

Their assumptions indicate that the utility of physicians in the presence of informative advertising would not change, meaning that it is exactly the same with and without informative advertising. Only persuasive advertising changes the physicians utility function. However, informative advertising also gives the advertised product an information advantage over products which are not advertised. Information advantages and information asymmetries are key issues in pharmaceutical markets.

Moreover, firms which invest in advertising might choose mixed advertising strategies, meaning it is difficult to disentangle persuasive from informative advertising. Advertising expenditures represent around 20% of a pharmaceutical firm's expenditures and are concentrated at the beginning of the product's life. Consequently, it makes more sense to assume that some physicians are more receptive than others to advertising. For the sake of simplicity, assuming that only two types of physicians exist, those that are receptive ("captured physicians") and those that are not ("non-captured physicians").

3.3.2 Impact of information advantages on the incentives to innovate

After a presentation of the motivation underlying the model (3.3.2.1), the framework and assumptions are described (3.3.2.2). By solving the model, two possible cases occur, depending on the innovation efforts, which are then analysed in detail (3.3.2.3) and allow for some conclusions to be drawn on the impact of reference pricing on incentives to innovate (3.3.2.4).

3.3.2.1 Motivation of the model

In this subsection, by adapting Königbauer's model assumptions, the purpose is to complete the benchmark model proposed by Ganuza et al. (2007, 2009) in order to analyse the impact of the introduction of a reference pricing scheme on incentives to innovate for pharmaceutical companies.

Thus, the presence on the market of an off-patent originator and its generic version will be taken into account as well as the impact of the information advantage of originators, and the imperfect agency between physicians and patients, on pharmaceutical firms' incentives to innovate.

Much like Ganuza et al., discussions regarding which form of reference pricing scheme is the most appropriate with regard to the criteria for clustering and setting the reference price will not be studied. Instead a general model of reference pricing will be used so that the results can be extended to every type of reference pricing scheme.

3.3.2.2 Framework and assumptions

Akin to the framework set by Königbauer (2007) and the model presented in the first part, consider a market for prescription drugs which consists of a continuum of patients distributed uniformly on the

segment $[0;\bar{t}]$. The patient's position on $[0;\bar{t}]$ can be interpreted as the extent to which the patient is ill and corresponds to a valuation for the treatment: $v(t) = t$. Hence, the more severely ill the patient is, the higher the willingness to pay. For the sake of clarity, $\bar{t}$ is normalised to 1.

Medicines can only be bought on prescription, so that the demand for drugs corresponds to the physician's prescription choice. As in the previous model, suppose that an information advantage (c) exists in favour of the originator product over its generic version. The physicians' valuation for the originator increases from t to ct with $c > 1$ due to this information advantage.

Furthermore, assume that the physicians who prescribe the drugs are heterogeneous in their preferences and are, as a result, more or less price elastic (Ganuza et al. 2007, 2009). Consider also that there is a group of physicians who are either of type 1 or 0. The group is normalised to 1 for simplicity reasons. Assume also that a proportion σ is of type 0 and the rest $(1-\sigma)$ of type 1. The proportion σ of physicians of type 0 is more receptive to the information advantage in favour of the original product than the $(1-\sigma)$ physicians of the other type, so that $c_0 > c_1 > 1$. The valuation of the treatment with the off-patent originator product B from the point of view of type i treating a degree of illness t can hence be written $c_i t$. The valuation of the treatment with the generic version from the point of view of any physician treating a degree of illness t is equal to t.

The annex 4 describes the variables present in the model.

1. Prescribing behaviour without a reference pricing scheme A type i physician prescribes the generic version to the patient when

$a+c_i t-\theta P_B < a+t-\theta P_G \Longleftrightarrow t < \frac{\theta(P_B-P_G)}{c_i-1}$ so that the demand for a generic (D_G) and the off-patent originator (D_B) by a physician of type i can respectively be written as:

$$D_G = \begin{cases} 1 \; if \; \hat{t} > t \Longleftrightarrow P_B - P_G > \frac{\bar{t}(c-1)}{\theta} \\ \frac{\theta(P_B-P_G)}{\bar{t}(c-1)} \; if \; 0 < \hat{t} < 1 \Longleftrightarrow 0 < P_B - P_G < \frac{(c-1)}{\theta} \\ 0 \; if \; \hat{t} < 0 \Longleftrightarrow P_B < P_G \end{cases}$$

and the demand for originator D_B as

$$D_B = \begin{cases} 1 \; if \; \hat{t} < 0 \Longleftrightarrow P_B < P_G \\ 1 - \frac{\theta(P_B-P_G)}{\bar{t}(c-1)} \; if \; 0 < \hat{t} < 1 \Longleftrightarrow 0 < P_B - P_G < \frac{(c-1)}{\theta} \\ 0 \; if \; \hat{t} > 1 \Longleftrightarrow P_B - P_G > \frac{(c-1)}{\theta} \end{cases}$$

Now, calculating the whole demand respectively addressed to the generic version and the originator, when $0 < D_{Gi}, D_{Bi} < 1$:

$D_G = \sigma\frac{\theta(P_B-P_G)}{c_0-1} + (1-\sigma)\frac{\theta(P_B-P_G)}{c_1-1} \Longleftrightarrow D_G = (\frac{\sigma}{c_0-1} + \frac{1-\sigma}{c_1-1})\theta(P_B - P_G)$

$D_B = 1 - (\frac{\sigma}{c_0-1} + \frac{1-\sigma}{c_1-1})\theta(P_B - P_G)$

2. Calculation of the profits Turning now to a calculation of the profits generated by the originator product and by the generic version. The profits can be written as:

$\Pi_B = P_B D_B = P_B(1 - (\frac{\sigma}{c_0 - 1} + \frac{1-\sigma}{c_1 - 1})\theta(P_B - P_G))$

$\Pi_G = P_G D_G = P_G(\frac{\sigma}{c_0 - 1} + \frac{1-\sigma}{c_1 - 1})\theta(P_B - P_G)$

Calculating the first order conditions to find the equilibrium prices:

$\frac{\partial \Pi_G}{\partial P_G} = 0 \Longleftrightarrow P_B = 2P_G$

and $\frac{\partial \Pi_B}{\partial P_B} = 0 \Longleftrightarrow 1 - (\frac{\sigma}{c_0 - 1} + \frac{1-\sigma}{c_1 - 1})\theta(2P_B - P_G) = 0 \Longleftrightarrow 1 - K\theta(3P_G) = 0$ with $K = \frac{\sigma}{c_0 - 1} + \frac{1-\sigma}{c_1 - 1}$

so that $P_G = \frac{1}{3K\theta}$ and $P_B = \frac{2}{3K\theta}$.

As $P_B - P_G = \frac{1}{3K\theta}$, it may be seen that, $D_G = K\theta\frac{1}{3K\theta} = \frac{1}{3}$ and $D_B = \frac{2}{3}$.

At the equilibrium, the profits of the originator firm are equal to $\Pi_B = \frac{4}{9K\theta}$ and these of the generic firm $\Pi_G = \frac{1}{9K\theta} < \frac{4}{9K\theta}$.

Thus, $D_B = 2D_G$, $P_B = 2P_G$ and $\Pi_B = 4\Pi_G$. The originator firm sells and earns more than the generic firm.

3. Prescribing behaviour with a reference pricing scheme Surmise that healthcare authorities decide to implement a reference pricing scheme. The reference price is set to the level of the price of the generic version. A physician of type i prescribes the generic version when

$a + c_i t - (P_B - P_G) - \theta P_G < a + t - \theta P_G \Longleftrightarrow t < \frac{P_B - P_G}{c_i - 1}$

As in the previous case without reference pricing, the demand functions for the off-patent originator and the generic version by a physician of type i may be calculated. Respective demand functions are equal to:

$D_{Bi} = \frac{1-(P_B - P_G)}{c_i - 1}$ and $D_{Gi} = \frac{P_B - P_G}{c_i - 1}$ for $0 < D_{Gi}$.

When calculating the whole demand addressed to the originator and the generic version, it may be seen that $D_B = 1 - (\frac{\sigma}{c_0 - 1} + \frac{1-\sigma}{c_1 - 1})(P_B - P_G)$ and $D_G = (\frac{\sigma}{c_0 - 1} + \frac{1-\sigma}{c_1 - 1})(P_B - P_G)$.

In turn, the respective prices and profits can be calculated as:

$\Pi_B = P_B D_B = P_B(1 - (\frac{\sigma}{c_0 - 1} + \frac{1-\sigma}{c_1 - 1})(P_B - P_G))$

$\Pi_G = P_G D_G = P_G(\frac{\sigma}{c_0 - 1} + \frac{1-\sigma}{c_1 - 1})(P_B - P_G)$

By calculating the first order conditions, equilibrium prices are found to be, respectively $P_G = \frac{1}{3K}$ and $P_B = \frac{2}{3K}$.

As $P_B - P_G = \frac{1}{3K}$, it may be ascertained that $D_G = K\theta\frac{1}{3K\theta} = \frac{1}{3}$ and $D_B = \frac{2}{3}$.

At the equilibrium, the profits of the originator firm are equal to $\Pi_B = \frac{4}{9K}$ and those of the generic firm $\Pi_G = \frac{1}{9K} < \frac{4}{9K}$

Results show that the demand, price and profits are the same as in the absence of a reference pricing

scheme with a price sensitivity of the physician θ, $\theta = 1$. By comparing the profits of both the originator and the generic firms, it may be concluded that profits are lower with a reference price scheme than without, due to the fact that $\theta \in [0; 1]$.

4. Incentives to innovate Now, assuming that firms have the ability to innovate and analyse the impact of a reference price on their incentives to innovate. While generics are copies of an originator product, originator companies have the facilities to invest in R&D, in order to increase the value of their product, compared to the existing therapies available. An improvement by a term δ leads to an increase of the utilities of both originator and generics.

Consequently, in the following equation it is inferred that the denominator $(c_i - 1)$ is reinforced by $(1 + \delta)$ and is equal to $(1 + \delta)(c_i - 1)$[16]. As a result, K becomes $K(\delta)$ and is equal to

$K(\delta) = \frac{\sigma}{(1+\delta)(c_0-1)} + \frac{1-\sigma}{(1+\delta)(c_1-1)} = \frac{K}{1+\delta}$.

The model is solved by backward induction. Prices and profits are defined first, then the pharmaceutical firm decides on the innovation effort it will make.

For $\delta > 0$, all prices and profits increase by the coefficient $(1 + \delta)$. As $P_G = (1 + \delta) \cdot \frac{1}{3K\theta}$ and $P_B = (1+\delta) \cdot \frac{2}{3K\theta}$, the profits of the originator and the generic firm are respectively equal to $\Pi_B = \frac{4(1+\delta)}{9K\theta}$ and $\Pi_G = \frac{(1+\delta)}{9K\theta}$.

Once the prices and profits are found, the innovation incentives as per Ganuza et al. (2007, 2009) may be modelled. Denote by $F(\delta, \gamma)$ the distribution function of δ, if an amount of γ is invested in R&D.

Furthermore, it is assumed that:

$\frac{\partial F(\delta,\gamma)}{\partial \gamma} < 0$ for $0 < \gamma < T$, and $\frac{\partial^2 F(\delta,\gamma)}{\partial \gamma^2} > 0$ (*)

i.e. a higher investment γ makes a bigger improvement δ more likely but at a decreasing rate(*). Given the second stage in which prices were calculated, the innovation decision is now analysed.

$\int_0^T \delta f(\delta, \gamma) d\delta - \gamma$ corresponds to the expected social surplus by an innovation investment of γ.

By partially integrating,

$\int_0^T \delta f(\delta, \gamma) d\delta = \delta F(\delta, \gamma) \mid_0^T - \int_0^T F(\delta, \gamma) d\delta = T - \int_0^T F(\delta, \gamma) d\delta$

The social optimum γ^* is hence characterised by $-\int_0^T \frac{\partial F}{\partial \gamma} d\delta - 1 = 0$. By taking into account the assumption $(*)$ made previously, the social optimum corresponds to the maximum.

The expected profits of B are equal to $E\Pi_B(\gamma) = \int_0^T \frac{4(1+\delta)}{9K\theta} f(\delta, \gamma) d\delta - \gamma$. After a simplification,

$E\Pi_B(\gamma) = \frac{4}{9K\theta} + \frac{4}{9K\theta} \int_0^T \delta f(\delta, \gamma) d\delta - \gamma = \frac{4}{9K\theta} + \Pi_B(\theta) \int_0^T \delta f(\delta, \gamma) d\delta - \gamma$.

The level of investment in innovation γ^B which maximises the profits of the originator company is characterised by:

[16] This is equivalent to multiply c_i with the coefficient β, with $\beta_i = 1 + \delta(1 - \frac{1}{c_i}) > 1$

$-\Pi_B(\theta)\int_0^T \frac{\partial F}{\partial \gamma}(\delta, \gamma^B)d\delta - 1 = 0$

For the level of investment in innovation γ^* which maximises the social optimum, then

$-\int_0^T \frac{\partial F}{\partial \gamma}(\delta, \gamma^*)d\delta = 1$ so that for γ^*, $\Pi_B(\theta) - 1 > 0 \Longleftrightarrow \Pi_B(\theta) = \frac{4}{9K\theta} > 1$.

The case where $\Pi_B(\theta) = 1 \Longleftrightarrow \gamma^B = \gamma^*$ is a special case.

Due to the assumptions on F, the integral is a decreasing function in δ. By multiplying by an absolute term higher than one to the negative of the integral, the left-hand side of the first order conditions shifts to the outside, here to the right. By contrast, the multiplication by a positive absolute term smaller than one shifts the left-hand side conditions to the inside, here to the left.

Consequently, two cases can occur:

- Case a): For $\frac{4}{9K\theta} > 1 \Longleftrightarrow \gamma^B > \gamma^*$meaning that the firm's innovation effort is too high compared to the optimal social innovation effort.
- Case b): For $\frac{4}{9K\theta} < 1 \Longleftrightarrow \gamma^B < \gamma^*$meaning that the firm's innovation effort is lower than the optimal social innovation effort.

Thus, case b) therefore ocurrs when $\frac{4}{9K\theta} < 1 \Longleftrightarrow \alpha < \frac{\sigma}{c_0 - 1} + \frac{1-\sigma}{c_1 - 1}$ with $\alpha = \frac{4}{9\theta}$. Both situations are now analysed.

Case a: Innovation efforts are higher than the social optimum The situation where the innovation effort is higher than the social optimum corresponds to the case where $\gamma^B > \gamma^*$ meaning that $\frac{4}{9K\theta} > 1$, with $K = \frac{\sigma}{c_0 - 1} + \frac{1-\sigma}{c_1 - 1}$. In this situation, it means that the term K is too small.

Policy methods to solve this issue would consist of increasing K or θ. Increasing K, with $K = \frac{\sigma}{c_0 - 1} + \frac{1-\sigma}{c_1 - 1}$ would mean either to decrease c_0 and c_1, and σ as $\frac{\partial K}{\partial c_0} < 0$, $\frac{\partial K}{\partial c_1} < 0$ and $\frac{\partial K}{\partial \sigma} < 0$. A higher heterogeneity of $(c_0 - c_1)$ leads to an increase of the term K. In practice, decreasing c_0 and c_1 would consist of decreasing the impact of advertising in the prescription choice of physicians. An example of such a policy would be a policy ban on advertising on new medicinal products. Decreasing σ would consist of normalising the practice of physicians, by, for example, creating a list of products to prescribe. They would be allowed to prescribe only the products present in the list. Such policies would lead to converge towards the optimal innovation effort. The implementation of a reference pricing would lead to increase θ to 1. Consequently, in the situation a, a reference pricing scheme would be beneficial to come closer to the social optimum.

This specific case was the example developed by Ganuza et al.. However, there is also another case to consider as it may be that the innovation efforts were already too low. This situation corresponds to the case b.

Case b: Innovation efforts are lower than the social optimum In this context, where the innovation effort is lower than the social optimum corresponds to a case where $\gamma^B < \gamma^*$ meaning that $\frac{4}{9K\theta} < 1$, with $K = \frac{\sigma}{c_0 - 1} + \frac{1-\sigma}{c_1 - 1}$. In this situation, the term K is too high. In this specific case, which is the contrary to the previous case, the policy tools to solve this issue would consist of decreasing K, which corresponds to increasing σ, c_0, or c_1.

Unlike the previous case, if the level of innovation by firms is lower than the social optimum, the implementation of a reference pricing scheme, which would increase the value of the term θ to 1, would only deteriorate the situation and increase the discrepancy between the social optimum of the innovation level and the private level.

5. Comparison of the cases with and without a reference pricing scheme Results show that the implementation of a reference pricing scheme corresponds to the case where the term θ takes its highest value, $\theta = 1$. Consequently, by increasing the value of θ to its maximum value, a reference pricing scheme also increases the probability for the case b' to ocurr. This can be shown in a figure.

Figure 3.4: Representation of the possible cases with and without a reference pricing scheme

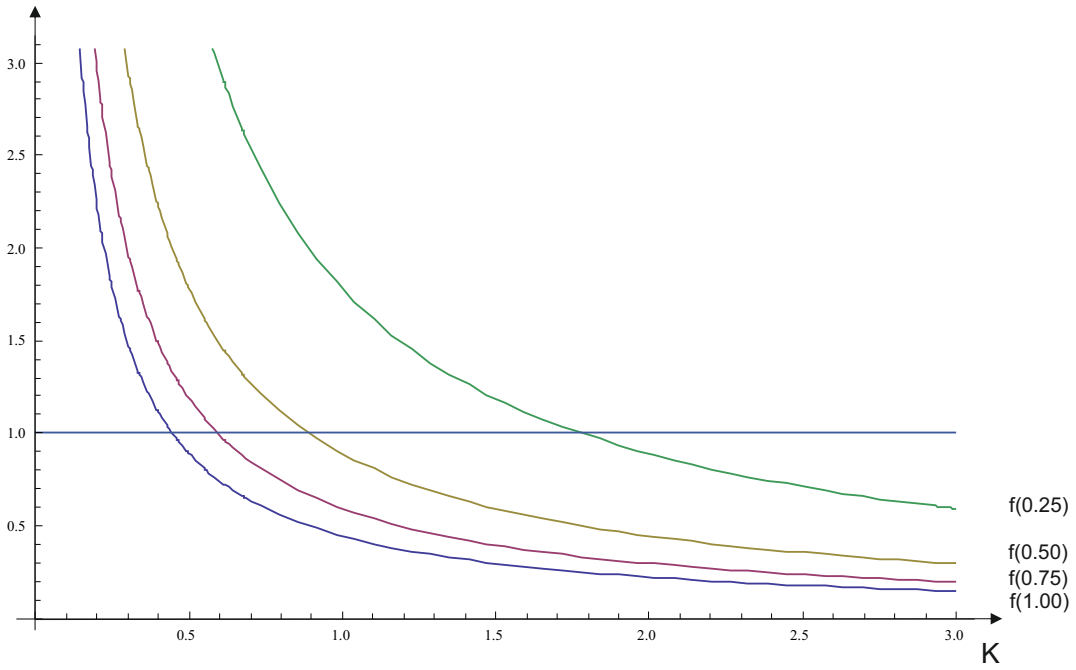


Figure 3.4 shows the representation of the function $f(\theta) = \frac{4}{9K\theta}$ for different values of θ. The value of θ is equal to one in the blue function (f(1.00)) which corresponds to the implementation of a reference pricing scheme. It is equal to 0.75 for the red one, to 0.5 for the yellow one and finally 0.25 for the green function. The X-axis corresponds to K (here between 0 and 3). Using the blue constant line which is equal to one, it is possible to see that for smaller values of θ, the likeliness of having $\gamma^B > \gamma^*$ is larger than in case of large values of θ. By increasing the value of θ to 1, its maximum, the implementation of a reference scheme increases the likeliness of the situation $\gamma^* > \gamma^B$ to take place. The implementation of a reference pricing scheme brings the innovation level closer to the social optimum, though it is not reached.

3.3.2.3 Conclusions of the model

These results partially counterbalance the findings of Ganuza et al. who exposed a bias towards small improvements in pharmaceutical companies' innovation incentives. The model shows that only when the innovation efforts are already too high, the implementation of a reference pricing scheme can be an adequate policy instrument in redirecting R&D expenses towards major innovations.

In that regard, results of the model differ from those of Ganuza et al. because the innovation efforts might be either too high or too low, depending on specific variables such as the value of perception and the physicians' prescription behaviour, as well as the advertising expenses of pharmaceutical companies. The results of Ganuza et al, only hold when the innovation efforts are too high. Otherwise, if they are too low as might happen in the model, the implementation of a reference pricing will increase the discrepancy between the social optimum of the innovation level and the private level.

Solutions, such as reference-pricing, to make the firm's incentives converge towards the first best solution, in terms of degree of innovation, consequently depends upon the initial situation, whether the level of innovation is already too high or too low. Healthcare authorities should first attain a good assessment of the situation, before deciding on the measures to take to strive towards a first best situation, in terms of degree of innovation. Thus, the implementation of a reference pricing scheme might be good or bad for innovation, depending on the initial level of effort to innovate. As a general conclusion on the model, the introduction of a reference pricing scheme does not represent a panacea. Its impact on the innovation efforts undertaken by pharmaceutical firms depends upon initial innovation efforts. Thus, depending on the policy objectives and the initial level of innovation, policy deciders should first ascertain a clear analysis of the circumstances before implementing a reference pricing scheme.

These different results come from the fact that it has been assumed that generic competition is present and furthermore the issue of advertising has also been introduced, which has a different impact on either

originators or generic manufacturers.

3.4 Policy implications and innovation incentives - Examples from Germany and France

Following the conclusions from the previous model, internal reference pricing does not represent the ideal instrument as it might have negative consequences if the innovation efforts are already too low. Even when its implementation is recommended, other factors (i.e. heterogeneity of physicians and advertising expenses among others) have to be taken into account, as they might either counterbalance or reinforce the expected effects. Other complementary measures are taken at the level of member states in off-patent markets, in conjunction with the implementation of a reference pricing scheme (3.4.1). This is because a reference pricing scheme also has an impact on innovation incentives that setting a special pricing and regulation framework for innovative medicinal products is to be taken into consideration by healthcare authorities (3.4.2).

3.4.1 Complementary measures in off-patent markets

Examples of complementary measures consist of normalising physicians' practices (3.4.1.1) and decreasing the impact of advertising (3.4.1.2).

3.4.1.1 Normalising the physicians' practices

In EU member states, different measures are employed to rationalise the prescription behaviour shown by physicians. In order to decrease the proportion of captured physicians σ, governments can offer them financial and non-financial incentives to prescribe cost-effective medicines, thus promoting the prescription of generics. In Germany, this corresponds to the performance audit (so-called "Wirtschaftlichkeitsprüfung")[17] based on the general efficiency rule (so-called "Wirtschaftlichkeitsgebot")[18] which requires for each physician's prescription practices to be "appropriate, sufficient, and necessary" ("zweckmässig, ausreichend und notwendig") in order to regulate the costs for health insurance funds. Indeed, in France, with regard to the promotion of the prescription of generics, article 19 of the Law n°2011-2012 on the strengthening of the safety of medicinal products also assures that the prescription of a medicinal product has to mention the INN of each product, which must be published on the pharmaceutical company's website.

Additionally, in France a contract was introduced with the object of improving physicians' practices, so-called CAPI within the Social Security Financing Law 2008 (so-called "Loi de Financement de la Sécurité

[17] Cf. par. 106, SGB V.
[18] Cf. par. 12, SGB V.

Sociale", LFSS 2008). The CAPI is a voluntary financial incentive designed, among other things to control physicians' prescribing behaviour. The objective of the CAPI scheme is to promote disease prevention, optimise the prescription of generic medicines and advocate less costly medicines, thus demonstrating equal efficiency (e.g. antibiotics, statins, antihypertensive medicines, PPI, antidepressants and ACE inhibitors). Such measures would be in the model employed analog to decreasing σ.

3.4.1.2 Decreasing the impact of advertising

In the matter of advertising, the 2011 French healthcare law n°2011-2012 restricts advertising and promotion by pharmaceutical companies in hospitals[19]. It provides limits to the visits made by pharmaceutical representatives in hospitals for an experimental two-year period. Visits are only allowed in the presence of several healthcare professionals. The system might be renewed, after an assessment report and extended timewise, as well as possibly encompassing the field of ambulatory medicines. Moreover, monitoring of pharmaceutical advertising was also strengthened, as a system of "prior visa authorisation" was implemented. Advertising of medicinal products is subject to prior review by the French Medicines Agency, ANSM[20]. Consequently, the advertising proposal submitted to the ANSM should meet specific criteria in terms of following the arrangements of the marketing authorisation, but also in presenting the medicinal product in an objective way, in promoting an appropriate use, and in not being misleading[21]. These measures would mean decreasing c in the current model.

By analysing the different policy instruments in place in France and Germany, it seems that they all endeavour to decrease advertising (c) and normalise the physicians' prescribing behaviour (σ) leading to an increase of the term K in this model. It means that governments assume that the level of innovation is already too high, compared to the social optimum (case b), and in this configuration a reference pricing scheme is relevant.

Role of the reference pricing scheme in the regulatory environment Reference pricing schemes which promote price competition in the generic market can also be used by healthcare authorities as a setback scenario to promote high value innovation for patients. It allows, by increasing the elasticity of demand, for the promotion of price competition in the generics market while contributing to a segmentation of the market for medicinal products between innovative and non-innovative, and/or not cost-effective medicinal products.

[19] Cf. Art. 30, Law 2011-2012

[20] Cf. Law 2011-2012, Chapter VII, art. 29-31 available at http://www.legifrance.gouv.fr/affichTexte.do?cid Texte=JORFTEXT000025053440&dateTexte&categorieLien=id, last accessed August 2012.

[21] Cf. new requirements on advertising for medicinal products available on the ANSM website, available at www.ansm.sante.fr/Activites/Publicite-pour-les-medicaments/Nouvelles-modalites-de-controle/(offset)/0, last accessed August 2012.

The second chapter showed that the definition of relevant markets performed by the EU within the pharmaceutical industry was bimodal. On the one hand, there are innovative and costly products which are available only by prescription, or mainly at a hospital, and are reimbursed. Then, on the other hand, less innovative pharmaceuticals (off-patent molecules), are cheaper and are often available OTC without a prescription and tending not to be fully reimbursed. The latter correspond to the products being included in reference pricing schemes.

3.4.2 Setting a special regulation framework for innovative products

Reference pricing schemes have an impact on firms' incentives to reach the socially optimal level of innovation by pharmaceutical companies. It is an indirect mechanism as, by excluding innovative products from the reference price, it indirectly impacts the pharmaceutical companies' incentive to innovate. A reference pricing scheme interacts with other measures focused at differentiating the regulatory framework between off patent markets and innovative markets.

The scheme's efficiency can thus be reinforced by specific measures, directed at patented markets, to value innovative medicinal products. While innovative medicinal products would be rewarded by a special framework in place, generic versions, or non-innovative products, would fall under the reference pricing scheme. Consequently, important pricing and reimbursement reforms took place which had an impact in particular innovative medicinal products in the EU. While the healthcare systems of Germany and France differ in their organisation and functioning, similar measures were taken in both countries for new drugs to prove their cost-effectiveness against active comparators for pricing and reimbursement purposes.

When implementing a policy targeting off-patent medicinal products, such as a reference pricing scheme, considerations surrounding innovation should also be taken into account, as patented products are also affected indirectly by this measure. Hence, an optimal policy design with the objective of raising innovation incentives should not only focus on measures affecting off-patent markets (so-called pro-generic policies), but first and foremost target innovative markets to reward innovative medicinal products. These new requirements which represent a hurdle to achieve market access for new firms, are a complementary tool alongside a reference pricing scheme in encouraging pharmaceutical companies to focus their R&D projects towards products which are more likely to be found innovative by healthcare authorities.

Germany: Introduction of price negotiation requirements for innovative products Reference pricing has been one major form of cost-containment in Germany, especially when it was extended in 2005 to therapeutically identical drugs which did not show any improvement in terms of effectiveness over

existing products (so-called "jumbo reference price groups")[22]. The pricing and reimbursement framework of innovative products underwent major changes with the "Act on the restructuring of the medicines market"[23], AMNOG reform, which was adopted in November 2011. It introduced from January 2011 onwards a new system of mandatory price negotiations with the GKV-Spitzenverband, the central body of the statutory health insurers, representing around 90%, and the principle of a HTA assessment for all innovative medicinal products, in the framework of a procedure of an early-benefit assessment (so-called "Frühnutzenbewertung")[24].

The procedure of early-benefit assessment which is performed by the HTA-body IQWiG[25] is a cost-effectiveness analysis. In this analysis, pharmaceutical companies are required to provide cost-effectiveness data to support their applications for reimbursement for innovative products in Germany. This cost-effectiveness analysis focuses on medicinal products that are brought to market for the first time (new molecule) or that receive a line extension (new indications). The procedure of benefit assessment described in the previous section turned into a regulatory hurdle for innovative medicines to reach the market.

In June 2012, the Joint Federal Committee, G-BA, decided upon the additional benefit of seventeen medicinal products. As of September 2012, only one company had reached an agreement with the GKV-Spitzenverband concerning the pricing of its new product. Four companies chose the "opt-out option" after the G-BA assessment on the cost-effectiveness of their medicinal products, which means that no price negotiation takes place and no price exists. These four products cannot be launched and sold in Germany which is an important outcome in the access to innovative treatments for patients[26].

The result of the G-BA decision on the additional benefit depends largely on the comparable therapy chosen by the G-BA to perform the assessment, as well as on the existing clinical studies. By investigating its practice, it seems that it selects the least costly therapy when choosing a comparator such as a generic medicinal product already priced at a low level. Therefore, it becomes very unlikely for the innovative product to be found more cost effective than the generic comparator. Moreover, during the price negotiations with the GKV-Spitzenverband, no possibility is foreseen for companies to present additional scientific data[27]. The consequence is that pharmaceutical firms become less keen on launching their

[22] Cf. art. 35. par. 1a of the Social Law Code (SGBV), available at http://www.jusline.de/index.php?cpid=f92f99b766343e040d46fcd6b03d3ee8&lawid=36&paid=35, last accessed August 2012.

[23] For more information, cf. website of the German Health Minister, available at http://www.bmg.bund.de/krankenversicherung/arzneimittelversorgung/arzneimittelmarktneuordnungsgesetz-amnog/das-gesetz-zu-neuordnung-des-arzneimittelmarktes-amnog.html, last accessed August 2012.

[24] Cf. art. 35a of the Social Law Code (SGB V).

[25] Cf. website of the IQWiG, https://www.iqwig.de/.

[26] Cf. website of the G-BA, http://www.g-ba.de/informationen/nutzenbewertung/, last accessed September 2012.

[27] Cf. Framework agreement of 10.4.2012 signed between the GKV-Spitzenverband and German pharmaceutical associations as foreseen in Art. 130b Nr. 9 SGB V, available at http://www.gkv-spitzenverband.de/media/dokumente/krankenversicherung_1/arzneimittel/rahmenvertraege/pharmazeutische_unternehmer Arzneimittel_Rahmenvereinbarung__130b_Abs9_SGB_V.pdf, last accessed September 2012. The framework agreement (Art. 6) provides as relevant criteria to set the price: the G-BA decision on additional benefit, the early benefit

product in Germany, due to the hurdles brought about by the procedure of early benefit assessment and the resultant limited perspectives in the matters of pricing and reimbursement. As for the choice of the appropriate comparative therapy, the G-BA assured that, in the future, it will provide a detailed explanation to justify the choice of the appropriate comparative therapy, in order to give pharmaceutical firms more predictability.

The reference pricing scheme remains an important pillar of the new pricing and reimbursement framework as it acts as a setback scenario for new products which need to prove their medical added value to be recognised as innovative and receive a high reimbursement price. Therefore, for a measure initially aimed at promoting generics, the reference pricing scheme has been refined and complemented in order to promote innovative medicines.

France: Price declaration for innovative products In France, a specific framework to reward innovative products and distinguish them from non-innovative ones is in place.

The Transparency Commission ("Commission de la Transparence") within the High Authority for Health (so-called "Haute Autorité de Santé") is the HTA-body[28] in charge of assessing the medical benefit of pharmaceuticals, so-called SMR, and the innovation level by assessing the improvement of the medical benefit, so-called ASMR, compared to alternative products and assessing the level of innovation offered by medicinal products[29]. The price setting decision of the pricing committee CEPS[30], is based among others on the ASMR rating granted by the Transparency Commission. Contrary to the SMR rating, the ASMR rating compares the therapeutic value of a pharmaceutical to the existing alternatives and assesses the improvement brought. ASMR ratings are regrouped in five main classes: ASMR I for medicinal products offering a major therapeutic value, ASMR II for medicinal products representing a significant improvement in terms of efficacy and/or reduction of adverse effects compared to existing alternatives, ASMR III for a modest improvement, ASMR IV for a minimum improvement and ASMR V for medicinal products without any therapeutic value, but still recommended to be registered on the positive list for reimbursement with

assessment conducted by IQWiG and the dossier submitted by the company, the annual therapy costs of comparable medicinal products and the 'actual sales price' in European countries in the country basket. Possible contractual arrangements with the GKV-Spitzenverband may include (amongst others, cf. Art. 4 VI): price-volume agreements/aspects, subsequent changes of the sales price. These further possibilities of contractual arrangements lead to flexibility for companies. Furthermore, these parts are confidential according to § 10 of the framework agreement (by contrast to the final rebate which is in the public domain).

[28] Cf. art. L162-17 of the Social Security Code http://www.legifrance.gouv.fr/affichCodeArticle.do?cid Texte=LEGITEXT000006073189&idArticle=LEGIARTI000020039241&dateTexte= and L5123-2 of the Public Health Code http://www.legifrance.gouv.fr/affichCodeArticle.do;jsessionid=95D2390DE3022CC0CF49921373FD520E.tpdjo15v_3?id Article=LEGIARTI000006689963&cidTexte=LEGITEXT000006072665&dateTexte=20100828, last accessed September 2012.

[29] Cf. art. L163-18 of the Social Security Code, http://www.legifrance.gouv.fr/affichCodeArticle.do;jsessionid =C901F8A489809034DAF6817E13C2273C.tpdjo07v_1?idArticle=LEGIARTI000021662904&cidTexte=LEGITEXT 000006073189&dateTexte=20100830, last accessed September 2012.

[30] Cf. CEPS website, http://www.sante.gouv.fr/comite-economique-des-produits-de-sante-ceps.html.

a price criterion which does not lead to any non-justified expenses.

For innovative products, a fast-track procedure of price setting has been provided by law since 2003[31]. Innovative pharmaceuticals are products with an ASMR I, II and III rating and IV under strict conditions[32]. In this fast-track procedure, right after the granting of the ASMR by the Transparency Commission, the manufacturer proposes a price that is de facto accepted, provided that the CEPS does not object to it within two working weeks. Otherwise, the normal application procedure applies, meaning that the price is negotiated between the pharmaceutical company and the pricing committee[33]. These new measures make marketing and reimbursement of innovative medicinal products in France harder, while giving pharmaceutical companies incentives to be more targeted in their choice of R&D projects.

However, these measures when applied to innovative pharmaceuticals, are relatively disconnected from the reference pricing scheme in place in France contrary to Germany. An explanation can be found in the fact that the implementation of the reference pricing scheme in France is more recent and, consequently, less developed than in Germany. In France, the rationale behind the reference pricing scheme remains mostly linked to the status of the patent and less to the innovation level examined in the HAS assessment. A closer link between the new measures and the reference pricing scheme could result in synergies, as in Germany and hence promote innovative medicinal products.

Conclusions and comparisons between both countries Germany and France have relatively different regulatory histories (price freedom/regulated price...) and different health systems (health insurance funds/main health insurer...). However, in both countries, the measures implemented progress in the same direction which is the implementation by HTA bodies of cost-benefit analyses for new products. Their aim is to define the benefit offered by a drug in order to set its price and its reimbursement level. However, they differ in the way they relate to existing regulatory frameworks, such as the reference pricing scheme. These measures share a common aim, i.e. to increase the differences that exist within the regulatory and pricing frameworks between innovative medicines and generics, or medicines being assessed as non-innovative. Hence, they are complementary with a reference pricing scheme and promote major innovation projects.

The examples of Germany and France show how the measures targeting off-patent and on-patent medicinal products are interdependent, and how they tend to segment pharmaceutical markets between in-

[31] Cf. Art. L162-17-6 of the Social Security Code, http://www.legifrance.gouv.fr/affichCodeArticle.do;jsessionid=5A01FF09C88782CD65E07B7B5DF9C877.tpdjo15v_3?cidTexte=LEGITEXT000006073189&idArticle=LEGIARTI000006741371&dateTexte=20100909&categorieLien=cid#LEGIARTI000006741371, last accessed September 2012.

[32] Cf. art. 7c) of the Framework Agreement, providing that pharmaceuticals with an ASMR IV rating are eligible for this fast-track procedure under two additional conditions. The first one is that a comparative pharmaceutical exists and that the price notified is lower than or equal as the price of the comparative product. The second additional condition is that the pharmaceutical does not replace a generic product or a product which is going to be genericised.

[33] For more information, cf. Natz and Campion., 2012a.

novative and cost-effective medicinal products and the rest of medicinal products which are non-innovative and/or not cost-effective. This conclusion is in line with the results of the econometric analysis of the market definition where it was observed that it was both segmented and exhibited a trend over time to an always narrower definition of the relevant product market.

CONCLUSION OF CHAPTER 3

Reference pricing schemes with different features are widely used in the EU among the member states. It has been shown that reference pricing schemes increase the price elasticity of demand and partially counterbalance the information advantage in favour of the off-patent originator. However, further measures are necessary to fully repeal the effect of the information advantage. This is the reason why complementary measures were put in place such as the implementation of collective visits in hospitals in France, or the recent anti-gift act in Germany.

Reference pricing schemes have, in the theoretical and empirical literature, a disputed impact on prices, profits, and the innovation incentives of firms. By focusing on the innovation incentives, it has been shown that reference pricing schemes can in some cases decrease the bias, due to the existing information advantage in favour of originators, and promote major innovations. Thus, reference pricing schemes do not only promote generics but also innovative medicinal products and, consequently, are complementary to other specific measures dedicated to innovative markets. By creating a different pricing and reimbursement framework for innovative and non-innovative medicinal products and in particular by excluding innovative medicinal products from being included in the reference price, reference pricing schemes represent a setback scenario for innovative medicinal products. This segmentation of pharmaceutical markets between innovative and non-innovative pharmaceuticals coincides with what was observed in the second chapter and led the EC to define always narrower markets.

Chapter 4

ECONOMICS OF RISK-SHARING SCHEMES IN PHARMACEUTICAL MARKETS

ABSTRACT OF CHAPTER 4

Risk-sharing schemes consist of agreements in on-patent markets between a pharmaceutical manufacturer and a health insurer to share the financial burden resulting from the uncertainty surrounding the pricing of innovative medicinal products. While these schemes exhibit different features across member states, two main schemes can be observed: performance-based risk-sharing schemes (hereinafter PBRSA) and volume-based risk-sharing schemes. In a performance-based risk-sharing scheme, the pharmaceutical company commits to granting a discount or paying back a certain amount when the effectiveness of the product is below a previously set threshold. In a volume-based scheme, also called a financial-based agreement, the pharmaceutical company commits to provide the product for free, when a certain volume is reached.

Once the implementation of such schemes has been reviewed in various member states, an economic analysis of risk-sharing schemes will be studied in order to analyse how they can be an instrument in solving the information asymmetries that exist in pharmaceutical markets - in particular hidden action and hidden information issues - when a pharmaceutical manufacturer has more knowledge on its product than the health insurer.

Modelisation shows that risk-sharing schemes can help in solving hidden action issues arising from the pharmaceutical companies' innovation efforts. By linking the price of the product to the outcome, pharmaceutical manufacturers are given continuous incentives to innovate on their product. In a signaling model, it can also be shown that risk-sharing schemes help in solving hidden information issues, when there is uncertainty in the effectiveness of innovative medicinal products. By modeling the contractual decisions as a signaling game, where the pharmaceutical firm can either offer standard contracts or risk-sharing schemes, it will be shown that the offer of a risk-sharing scheme signals a product of high-quality.

The third inquiry in the introductory chapter focused on how member states could offer patients timely access to innovative medicinal products, while preserving the equilibrium of their health care budgets. The use of so-called "risk-sharing schemes" between health insurers and pharmaceutical companies is an example of a widespread approach implemented to share the financial risk of uncertainty surrounding the effectiveness of innovative medicinal products.

Once the features of risk-sharing schemes in selected member states have been defined and described (4.1), the impact of such schemes on moral hazard issues with regard to innovation efforts (4.2) and adverse selection issues in respect to the effectiveness of new products (4.3) will be analysed.

4.1 Definition and rationale of risk-sharing schemes

First, the significant characteristics of the two main types of risk-sharing schemes are reviewed (4.1.1), after which a systematic review of the literature dedicated to risk-sharing schemes in pharmaceutical markets is then performed (4.1.2), and finally, the practice of selected member states in terms of risk-sharing agreements is investigated (4.1.3).

4.1.1 Definition and use of risk-sharing schemes

To solve the uncertainty in respect of the effectiveness of a product and its target population, risk-sharing agreements can be implemented between a pharmaceutical company and the payer. In these agreements, the pharmaceutical manufacturer guarantees the product's effectiveness in return for reimbursement (performance-based risk-sharing schemes) or commits not to sell more than a certain quantity according to the health care budget (volume-based risk-sharing schemes).

Risk-sharing schemes are defined in the literature as

> "agreements concluded by payers and pharmaceutical companies to diminish the impact on payers budgets for new and existing schemes brought about by uncertainty and/or the need to work within finite budgets" (Adamski et al. 2010).

Risk-sharing schemes consist of formal arrangements between payers and manufacturers with the objective of sharing the financial risk due to uncertainty surrounding the introduction of new products, in particular with the constant increase in the last decades of pharmaceutical prices and of the payments by healthcare insurers (see figure 4.1).

Health insurers: Risk-sharing schemes to manage uncertainty Methods of in-market evidence generation through health economic assessment are often insufficient in providing complete information

Figure 4.1: Industry key data (1990-2008)

INDUSTRY (EFPIA total)	1990	2000	2012	2013
Production	63,010	125,301	213,003	217,500 (e)
Exports (1) (2)	23,180	90,935	312,377	316,500 (e)
Imports	16,113	68,841	224,811	226,500 (e)
Trade balance	7,067	22,094	87,566	90,000 (e)
R&D expenditure	7,766	17,849	30,035	30,630 (e)
Employment (units)	500,879	534,882	693,195	690,000 (e)
R&D employment (units)	76,126	88,397	115,196	115,000 (e)
Pharmaceutical market value at ex-factory prices	41,147	86,704	160,574	163,000 (e)
Pharmaceutical market value at retail prices	64,509	140,345	237,240	240,800 (e)
Payment for pharmaceuticals by statutory health insurance systems (3)	40,807	76,909	119,345	119,950 (e)

Sources: EFPIA, 2014

on a new product. There has always been uncertainty about real-world clinical and economic performance around a new product from the health insurer's side. However, with the emergence of new technologies and new types of often costly products (biologics, diagnostics...), this uncertainty has escalated tremendously. Payers are increasingly concerned about "decision uncertainty", that the product might not be cost-effective compared to existing alternatives (Towse et al., 2010; Antonanzas et al., 2011). Thus, Cook et al. (2008) compare risk-sharing schemes to warranties, which are used by pharmaceutical companies to inform health insurers of the quality of their product which is not fully observable, in particular with regard to innovative and costly medicinal products. Therefore, in this situation of moral hazard, pharmaceutical companies provide assurance to the health insurer.

The origin of the uncertainty around innovative medicinal products is to be found in the health insurer's lack of information on real effectiveness and the budget impact of new drugs. These issues around uncertainty are behind the implementation of risk-sharing schemes. As previously explained the likelihood of success of a medicinal product, meaning its probability to heal the patient, was originally tested during clinical trials, ex-ante. However, these tests are performed on a certain population, chosen according to specific criteria, which might differ from that of real patients. Thus, the real ex-post product's effectiveness might vary from the efficacy tested in clinical trials depending for example on the sub-population treated

or on certain specific patients.

Pharmaceutical firms: Signaling the effectiveness of their product in the presence of information asymmetry For pharmaceutical firms, assessing the effectiveness of their product is often costly, time-consuming and removed from the real-world aspects of treatments (Hunter et al., 2010). Consequently, pharmaceutical companies accept risk-sharing schemes to receive reimbursement coverage in order to build trust and good faith in their new product from the payer and to prove their therapeutic value via real-world evidence. Moreover, pharmaceutical drugs are experience goods, hence complete information on the product before it is marketed and used is not feasible. For these reasons, health insurers' coverage decisions contain a degree of uncertainty which can be resolved through usage.

Cook et al. (2008) explain that pharmaceutical companies - as manufacturers of the product - are in a better position to have greater insights into the performance brought by their product. To alleviate part of the risks, the pharmaceutical company might accept that, if a certain threshold of performance or a particular outcome is not reached, the price of the product will be reduced or the product will be provided for free.

Such agreements are also important for pharmaceutical companies to maintain a high list price. This is significant for manufacturers as the price of a product is often used as a basis for other cost-containment measures, such as external reference pricing where the product's price in a certain country is pinned to its price in a basket of countries.

For pharmaceutical companies, this kind of money-back guarantee is also a means of addressing new payers' hurdles at an early stage of the life cycle. Risk-sharing represents an instrument for pharmaceutical companies in order to overcome the payer's aversion to the risk of uncertainty while decreasing the time to market access.

4.1.2 Characterisation of risk-sharing schemes

Different typologies of risk-sharing schemes exist. However, two types of risk-sharing schemes, performance-based and volume-based risk-sharing schemes can be differentiated (4.1.2.1). The example of a performance-based risk-sharing scheme in the UK will be described in more detail (4.1.2.2).

4.1.2.1 Performance-based risk-sharing schemes and volume-based risk-sharing schemes

Performance-based risk-sharing schemes Performance-based risk-sharing schemes are arrangements where the company refunds the payer if the drug's desired outcome is not reached (Towse et al., 2010). In this framework, "drugs are paid for only to the extent that they work" (Lilico, 2003). De Pouvourville

(2006) also notes that a performance-based risk-sharing scheme consists of: "a contract between two parties who agree to engage in a transaction in which there are uncertainties concerning its final value. Nevertheless, one party, the company, has sufficiently confidence in its claim of either effectiveness or efficiency that it is ready to accept a reward or a penalty depending on the observed performance".

With regard to the refunding of health insurance, different mechanisms are implemented, ranging from price adjustments, to delivery free of charge in cases where the patient does not respond to treatment.

Volume-based risk-sharing schemes With a volume-based risk-sharing scheme, a product is only reimbursed until a certain ex-ante defined threshold of sales is reached. Price-volume agreements usually focus on controlling budget expenditures and contain a clawback provision, as is the case in France. The purpose of such schemes is to ensure that the additional expenditure linked to the product's reimbursement does not increase above a pre-established amount. Such schemes are attractive to health insurers as a means of avoiding that the population treated with the product exceeds the expected target population.

In the following sections, the main focus will be on the uncertainty surrounding the effectiveness of the product. For this reason, the following analysis will concentrate on performance-based risk-sharing schemes.

4.1.2.2 Example of a performance-based risk-sharing scheme: The "Velcade Response Scheme"

One well-known risk-sharing agreement is the "Velcade Response Scheme". The product Velcade®[1] by Johnson & Johnson, which was recommended in the treatment of relapsed multiple myeloma without bone transplantation, was considered by the UK health care authorities NICE as cost-ineffective with regards to the ratio of its performance compared to the related costs. The product was, however, made available for patients in 2007 with the implementation of a risk-sharing scheme (so-called "Velcade Response Scheme", VRS). The product could then be prescribed and reimbursed under the specific conditions set in the agreement.

These conditions concerned the subgroups of patients to be treated as well as the price of the product. Indeed, only patients suffering from progressive multiple myeloma with a first relapse having already tried one therapy and when a bone transplant was not an option, were eligible to be treated with Velcade®. Prescribing physicians also received clear guidelines from NICE detailing when Velcade should be prescribed (Hunter et al., 2010).

[1] Cf. "Risk-Sharing Practices and Conditional Pricing of pharmaceuticals- How to deal with uncertainty? - Some EU Member State practices" and velcade.co.uk.

With regard to the price of the product, the risk-sharing agreement foresaw that after four weeks of treatment the result was to be assessed by a serum protein test. The test was considered a success when the serum proteins were reduced by 50% or more. In this case, the treatment could be continued and was fully reimbursed by the UK health care insurer, the NHS. If the result was under the set threshold, the treatment was considered as inefficient and was stopped. In this outcome, the pharmaceutical company committed in the agreement to refund the NHS (Adamski et al., 2010).

4.1.3 Insights into the utilisation of risk-sharing agreements in selected member states

The general features and the regulatory basis of risk-sharing agreements differ among member states. Practices in Italy (4.1.4.1), the UK (4.1.4.2), Germany (4.1.4.3), and France (4.1.4.4) will be now briefly described.

4.1.3.1 Italy: Proactive in implementing innovative risk-sharing schemes for oncology drugs

The role of the Italian Medicines Agency (AIFA) and monitoring registries Italy is one member state which has widely implemented risk-sharing schemes driven by the Italian Medicines Agency AIFA[2] on a case-by-case basis for new innovative medicinal products presenting uncertainties with regards to their effectiveness and/or budget impact. For this reason, AIFA implemented conditional reimbursement schemes together with the creation of Monitoring Registries ("Registro Farmaci Oncologici sottoposti a Monitoraggio") to collect data on the effectiveness and safety of new pharmaceuticals.

The aim of these online patient registries is to ensure the eligibility of patients, assess the medicinal product in practice, collect missing data and control the overall budget. The indications concerned by these registries are mainly oncology, diabetes, psoriasis, and orphans. By the end of 2012, these monitoring registries oversaw seventy-eight therapeutic indications, including twenty-eight which contained a conditional reimbursement mechanism (Kanavos, 2013). Three types of conditional reimbursement mechanisms can be differentiated. While they all imply a certain health outcome, their differences lie in the financial arrangement. In so-called "cost-sharing" arrangements, a general discount is applied for all eligible patients at the start of the treatment until it becomes clear if the patient is responding or not. The difference between "payment by results" and so-called "risk-sharing" schemes is that under a "payment by results" scheme the pharmaceutical firm will reimburse the full cost of the treatment for patients that do not respond to treatment. Under a so-called "risk-sharing scheme", a discount is calculated and the pharmaceutical company only pays back around 50% of the costs.

[2]Cf. http://www.agenziafarmaco.gov.it/.

Examples of schemes implemented in Italy The first example of a payment by results is Nexavar (2009) which was refused in the UK for patients suffering from kidney and liver cancer because of its lack of cost-effectiveness, but was accepted for reimbursement in Italy as a second-line treatment of advanced renal cell carcinoma under specific conditions. The agreement was that AIFA would receive a 50% discount during the first three months and then the product was fully reimbursed, but only for patients that responded. In order to monitor the number of patients and clinical outcomes, a "register of oncology medicines", so-called "Registro Farmaci Oncologici sottoposti a Monitoraggio", was set up in December 2005 to allow for the monitoring of the whole process, from the patient's diagnosis, to the drug delivery.

Another example of a risk-sharing scheme is the active ingredient panitumunab (2009), which required pharmaceutical manufacturers to pay back 50% of the costs for patients that did not respond after an evaluation treatment of two months[3].

4.1.3.2 United Kingdom: The role of NICE and "Patient Access Schemes"

Role of "Patients Access Schemes" ("PAS") The health care system in the UK is based on the tax-funded NHS[4]. Since 2009 risk-sharing schemes are negotiated within the framework of the PPRS which consists of a five year non-contractual voluntary scheme. An evaluation by the OFT in 2007 indicated two cases in which risk-sharing schemes were implemented. The first case is "where data at the time of launch is insufficient to take an informed view on cost-effectiveness" (OFT, 2007, p.6). The second case deals with situations when "the appraising body determined that there was sufficient uncertainty about outcomes, there would be an opportunity to consider risk-sharing schemes or 'only in research´recommendations' (OFT, 2007, p. 107). Prior to 2009, risk-sharing schemes were implemented, i.e. the "Multiple Sclerosis Risk-Sharing Schemes", but without any regulatory framework.

In the 2009 PPRS, two types of risk-sharing schemes can be defined, outcomes-based risk-sharing schemes and financial-based risk-sharing schemes. In the financial-based scheme, the price of the product is not altered but the firm will offer a discount based, for example, on the number of patients treated, or the number of patients that responded to treatment. As for an outcomes-based scheme, different sub-types exist with their own characteristics: proven value, price increase, expected value rebate and so-called risk-sharing. The common point of these four sub-types is to finance only effective medicinal products (EMINET, 2011).

NICE plays a key role by issuing an ex-ante cost-effectiveness analysis, performing ex-post reviews and deciding on the appropriate risk-sharing scheme. To be considered in a PAS, the product will be included

[3] More information on the various types and the specific features of the different conditional reimbursements granted by the AIFA can be found at the following webpage: http://antineoplastici.agenziafarmaco.it/, last accessed August 2013.

[4] Cf. www.nice.co.uk.

in a positive NICE guidance. PAS are always proposed by the manufacturer and might be accepted as a part of the NICE assessment process, on the conditional approval of the DoH, and a positive guidance issued by NICE. Final terms are negotiated by the DoH on the basis of NICE's assessments. The aim of these PAS is to facilitate patient access to innovative medicinal products which, due to the uncertainty of their cost-effectiveness, would not otherwise have been recommended by NICE.

Example of schemes implemented in the UK In addition to the "Velcade Risk-Sharing Scheme" example, in the case of Tarceva® (erlotinib), which is used to treat non-small cell lung carcinomas, a risk-sharing scheme was implemented as a result of the uncertainty around the effectiveness of the product. The aim of the scheme providing a 14.5% discount was to equalise the costs of the treatment using Tarceva® with the comparator Docexatel®.

Another example is Stelara® (ustekinumab), which is used to treat severe plaque psoriasis. As for Tarceva®, a risk-sharing scheme was implemented as a result of the uncertainty around the effectiveness of the product. In the case of Stelara, the pharmaceutical manufacturer agreed to provide the higher dose required for patients weighting more than a hundred kilos at the same price as the lower dose for patients weighting less. This was therefore equivalent to sell two units of the product for the price of one.

4.1.3.3 Germany: Schemes at regional or individual health insurer fund levels

Role of health insurance funds ("gesetzliche Krankenkassen") in the introduction of risk-sharing schemes Risk-sharing schemes in Germany and France are not as well established as in Italy and in the UK. Before the "Act on the restructuring of the medicines market"[5], AMNOG, which was adopted in November 2011, price setting of medicinal products in Germany was unregulated. From January 2011 Germany introduced a new system of mandatory price negotiations with the central body of the statutory health insurers representing around 90% of health insurance funds (so-called "GKV-Spitzenverband"[6]) and the principle of a HTA assessment for all innovative medicinal products in the framework of a procedure of an early-benefit assessment (so-called "Frühnutzenbewertung")[7].

Based on the "Law increasing competition among the health insurance funds", the GKV-WSG[8], which introduced competition among the different health insurance funds and allowed them to negotiate contracts and rebates directly with pharmaceutical manufacturers, risk-sharing agreements mainly take place at the level of each health insurance fund. Before the GKV-WSG was implemented, pharmaceutical

[5]For more information, cf. website of the German Health Minister, available at http://www.bmg.bund.de/krankenversicherung/arzneimittelversorgung/arzneimittelmarktneuordnungsgesetz-amnog/das-gesetz-zu-neuordnung-des-arzneimittelmarktes-amnog.html, last accessed August 2013.

[6]Cf. website of the GKV-Spitzenvervand, http://www.gkv-spitzenverband.de/.

[7]Cf. art. 35a of the Social Law Code (SGB V).

[8]For more information on the GKV-WSG, cf. http://www.buzer.de/gesetz/7655/index.htm.

manufacturers were required to negotiate directly with the Federal Joint Committee, the G-BA[9]. Due to this fragmentation of agreements, the available information on such schemes is not centralised, nor was it handled in a transparent way. Kanavos et al. (2013) identified a total of fifteen risk-sharing schemes.

Example of the Avastin agreement In the field of oncology, an agreement was negotiated in 2007 between the manufacturer of Avastin® and several health insurance funds to administer this anti-cancer drug together with Taxol®, a chemotherapy product. The purpose of the performance-based agreement was to test whether the co-administration of both products might increase the patient's survival in cases of metastatic breast cancer and metastatic renal cell carcinomas. In the agreement, the pharmaceutical firm committed to pay back fully or partially in cases where the treatment exceeded the total dosage over a predefined period. Espin et al. (2011) explained that no extension of survival has been proven through the combination of both products. Espin et al. also noted that these unsuccessful results are mostly the consequences of a breach in the treatment, due to complications or toxicity issues resulting in several patients not reaching the total predefined dosage.

4.1.3.4 France: Role of the Health Care Products Pricing Committee ("CEPS") and traditional price-volume agreements

Legislative and regulatory framework In France, it is the pricing committee CEPS[10], which consists of officials from different ministries and health insurance funds, that is in charge of the pricing of medicinal products. The CEPS negotiates with the French pharmaceutical association LEEM ("Les Entreprises du Médicament", hereinafter LEEM)[11] in line with the ministerial policy of a so-called "framework agreement" (so-called "accord-cadre") to set prices[12]. The CEPS is also entitled to sign directly with pharmaceutical companies a contractual agreement for a maximum of four years. The ex-factory price set by the CEPS is based on the ASMR rating of the Transparency Commission, the expected sales of the medicinal product, the price of the products in other EU member states, and the prices of existing alternatives. However, the final price paid to pharmaceutical firms varies due to the existence of clawbacks, price review clauses and contractual agreements.

Clawback per pharmacotherapeutic class and based on capped turnover In case the sales exceed the national objectives on health care spending ("Objectifs Nationaux des Dépenses d'Assurance

[9] Cf. Natz and Campion, 2012a.
[10] More information available at http://www.sante.gouv.fr/comite-economique-des-produits-de-sante-ceps.html.
[11] For more information, cf. www.leem.org.
[12] The framework agreement which was signed on 5 December 2012 and covers i.a. sales growth, pricing and promotion, is available at http://www.sante.gouv.fr/IMG/pdf/accord_cadre_du_051212.pdf, last accessed August 2013.

Maladie", hereinafter ONDAM) which are defined each year in the LFSS, article seventeen of the framework agreement provides for the so-called "safeguard clause" by means of clawbacks[13]. As this clause is included in the framework agreement, it is binding for all pharmaceutical companies that are a member of the LEEM, hence the majority of French pharmaceutical companies. To this purpose, at the end of the year, pharmaceutical companies notify the CEPS of their annual volume and turnover of sales for each medicinal product and pharmaceutical form. The application of clawbacks corresponds to the payments per pharmacotherapeutic class as well as payments based on the reported turnover of the pharmaceutical firm[14].

The objective of these clawbacks is to limit the budget impact of the delivery of a medicinal product for non-approved indications. In addition to the application of clawbacks, two types of price review clause also exist which lead to a revision of the initial price set by the CEPS[15]. The first corresponds to a "daily treatment clause", which provides for an adjustment of the price when the time and usage of a medicinal product are not in accordance with what was assumed at the time of the price-setting and result in a higher real cost per patient than expected. The second type of condition covers "volume clauses", its purpose is to ensure that the medicinal product's volume of sales remains in line with the expected target population. Prices might also be updated at the initiative of the CEPS when the product's registration is renewed, or when new scientific data is available. This framework does not cover the agreements based on clinical results which are scarce.

Kanavos et al. (2013) mention two examples of agreements signed in 2008 involving the products Naglazyme®, for the treatment of mucopolysaccharide type VI disease, and Soliris® which is indicated for the treatment of paroxysmal nocturnal haemoglobinuria. The agreements provided that above a certain threshold of sales set beforehand in the agreement, the pharmaceutical firms manufacturing both products committed to supply the product free of charge, while paying back any turn-over above the threshold.

Performance-based risk-sharing schemes in a limited number of examples While volume-based risk-sharing schemes are provided for in the framework agreement, which is a legal document, performance-based risk-sharing schemes have also been implemented in a very few number of cases. These cases involved medicinal products which have been granted a low ASMR rating and claimed that the rating did not reflect the effectiveness of the product, which can only be verified by use.

[13] Cf. article 17, Annual financial regulation, available at http://www.sante.gouv.fr/IMG/pdf/accord_cadre_du_051212.pdf, last accessed September 2012.

[14] Please note that specific provisions are foreseen in article 18 of the framework agreement for innovative medicinal products which are exempted from a clawback for a certain period of time depending on the ASMR granted by the Transparency Commission. More information is available at http://www.sante.gouv.fr/IMG/pdf/accord_cadre_du_051212.pdf.

[15] See Art.L162-17-4 of the Social Security Code, available at http://www.legifrance.gouv.fr/affichCodeArticle.do?cidTexte=LEGITEXT000006073189&idArticle=LEGIARTI000017828253&dateTexte=, last accessed September 2012.

Kanavos et al. (2013) listed the restricted conditions to be fulfilled for the pharmaceutical company to obtain such an agreement. Among the conditions, the company must prove that only real use of the medicinal product can provide evidence on its effectiveness, that the product represents a real advantage among the available treatments, and finally that if the effectiveness claimed is not proven by use, the pharmaceutical firm is ready to bear the financial risk. If the product's performance is proven, then the negotiated price is upheld.

The first reported performance-based risk-sharing scheme in France, which involved an oncology product, was not disclosed due to a confidentiality clause in the agreement. One example of such an agreement concerned the drug Risperdal®, which is used to treat schizophrenia. The conditional price was granted based upon the drug's results from 2006 to 2013. The pharmaceutical company claimed that the product would lead to more patients compliance which would decrease the number of hospital admissions. If the results of the data gathered do not lead to a higher ASMR rating, the pharmaceutical company is obliged to pay back the difference for the previous years of use and get a reduced price for the years to come. The use of Risperdal® supported the pharmaceutical company's claim (Garrison et al. 2013). With the implementation of the new medicinal products law in December 2011, which requires medico-economic evaluations for the reimbursement application of every new product, the trend towards performance-based risk-sharing schemes to gather data on the ASMR rating is likely to increase.

4.1.4 Review of the theoretical literature

The theoretical literature on risk-sharing schemes implemented in pharmaceutical markets is relatively scarce. The existing papers focus on the impact of such agreements on prices and pharmaceutical companies' profits.

Lilico (2003) Lilico (2003) investigated in his paper the conditions under which a performance-based risk-sharing agreement is desirable. In his model, Lilico differentiated between cases where the pharmaceutical company sells the treatment (usual price-setting) from where it sells the cure (risk-sharing scheme) depending on whether the patients are risk-adverse or risk-neutral. He found that a risk-sharing scheme can be considered as a transfer of risks from patients who are risk-adverse to companies which are risk-neutral. In his model, the gains of risk-sharing are higher, the more risk-adverse the patients are, the more serious the disease, and the lower the success of the treatment.

Lilico also stressed that the costs of monitoring will in general outweigh the benefits of the scheme. For these reasons, risk-sharing schemes are only desirable for new expensive treatments. Indeed, only where expensive treatments are involved, the costs of monitoring are relatively small in comparison to

the total treatment costs. In an extension of his model, Lilico also investigated the circumstance where additional patients with a lower success probability are treated, when the health insurer is not more risk-adverse than the pharmaceutical company, and analysed the impact of such schemes on pharmaceutical companies' incentives to innovate.

Zaric et al. (2005, 2009) Zaric et al. (2005) offered further context by observing that payers are not only concerned with the uncertainty of the product's cost-effectiveness but also by the unlimited financial risk borne by the health insurance, when the demand for the innovative product is higher than expected once the product is added to the reimbursement list. They stressed that demand might be higher than expected by the health insurer due to the presence of marketing efforts arising after the product is listed. A higher demand has important consequences on the equilibrium of health care budgets. Therefore, they assumed that payers implement a risk-sharing scheme to hedge against uncertainty, with regard to the total number of patients treated with the innovative product, and analysed it according to the model of a price-volume agreement based on the total budget. They concluded that a single price-volume agreement with specific fixed features would not be optimal as the results depend on variables such as the price or the rebate proportion. Consequently, the features of the optimal risk sharing agreement vary dependent upon these variables.

Zaric et al. (2009) further analysed in a two-stage model, two different performance-based risk-sharing schemes whose purpose is to alleviate the risk borne by the health insurance with regards to the product's effectiveness. In the first scheme, the product is no longer reimbursed if it is not effective, while in the second scheme, the price of the product is only reduced by a rebate in the second stage, if it is found to be ineffective. Zaric et al. showed that neither arrangement is to be preferred by pharmaceutical companies as several factors must be taken into account when selecting the arrangements, especially the efficacy (also called "expected effectiveness") and the real effectiveness of the drug. They stressed that the arrangements place different incentives on the pharmaceutical company. However, they also observed that their model suffers from an important limitation as it does not take into account the monitoring costs inherent to performance-based agreements, which may be important and may influence the results.

Capri et al. (2011) Capri et al. (2011) analysed the price and the expected profits from different performance-based risk-sharing agreements based on the effectiveness of the drug in real use (by contrast to the efficacy, also called the expected effectiveness). They showed that the number of patients treated is not necessarily affected by the risk sharing agreement, but that industry profits are always lower with the implementation of a risk sharing agreement and are dependent on the pharmaceutical companies'

bargaining power.

Barros (2011, 2013) Barros (2011) investigated the economic fundamentals of risk sharing schemes and discussed the various benefits and costs related to the implementation of risk-sharing agreements. Barros explained that such schemes have two different goals: firstly, for health insurers, a risk-scheme enables them to treat more patients who exhibit a low probability of being cured by the treatment, without significantly affecting the health care budget. Secondly, for pharmaceutical companies, such schemes can be used as signaling effects, as only those companies with a sufficiently high degree of confidence in their product will accept such a scheme. Barros' objective was to define the conditions under which risk-sharing schemes are advantageous for both health care authorities and pharmaceutical companies. His analysis showed that the effects of a risk-sharing scheme are ambiguous, as too many patients might be treated and prices might increase as a result of the anticipation of future similar schemes. For these reasons, the impact of risk-sharing schemes on social welfare is uncertain. Since too many patients exhibiting a low likelihood of finding a cure might be treated, a risk-sharing scheme might indeed lead to an increase in the costs for the health insurer depending on the design of the scheme. In an extension to this model, Barros also analysed the impact of a risk-sharing scheme on pharmaceutical companies' incentives to innovate and the interaction between those incentives and detailing activities, both performed to increase the value of the new treatment.

Barros (2013) further analysed the impact of a risk-sharing scheme on the consumer's surplus and the expected profit of pharmaceutical companies by taking into account the number of target patients as constant and the existence of a listing process for pharmaceutical products. The listing process considered by Barros depends on the difference between the cost-effectiveness of the new medicinal product and the maximum costs the society is willing to pay for the new drug. In this framework of analysis, a risk-sharing agreement based on the ex-post effectiveness of the product is proposed by the pharmaceutical manufacturer to the health insurer. The health insurer might accept it and makes the product available in the list of reimbursed products, or not. The decision of the health insurer is assumed to be based on the expected cost-effectiveness of the medicinal product. Barros found that, while the price of the product is expected to decrease, the impact of the risk-sharing scheme depends on the listing process decision of the health insurer. The parameters related to the listing process of the health insurer as well as the impact of the risk-sharing scheme on the listing process are key variables which influence the expected profit of the firm in both directions.

Antonanzas et al. (2011, 2013) Antonanzas et al. (2011) investigated when health care authorities implemented a performance-based risk-sharing agreement in the presence of uncertainty on the effectiveness of a product. They explained that health care authorities face uncertainty, mainly focused on the effectiveness and the safety of the product, the rate of substitution, the size of the population to be treated and the growth of the disease's prevalence, when making their pricing and reimbursement decisions. In their model, which is based upon Barros' model (2011), they focused on the uncertainty surrounding the effectiveness of the product and compared the situation with and without risk-sharing schemes. The aim of their paper was to find the conditions under which each type of contract will be preferred by the health insurer and the pharmaceutical company. They found that the optimal contract depends on a trade-off between the monitoring costs, the marginal production costs and the utility derived from the treatment. Risk-sharing schemes are mainly to be used when the monitoring costs are low enough.

Antonanzas et al. (2013), by comparing a traditional price-setting and a performance-based risk-sharing scheme, showed that the design of an optimal risk-sharing agreement depends on a trade-off between different parameters such as the monitoring costs, the marginal production costs, as well as the costs in terms of patients' loss of well-being in case of product failure. In their analysis, a risk-sharing agreement is always prefered by the health insurer when the expected effectiveness of the new medicinal product is low due to cost-effectiveness considerations.

Further research Theoretical literature on risk-sharing schemes is scarce and is largely focused on performance-based agreements. Risk-sharing agreements are negotiated to alleviate financial risks related to the ex-post effectiveness of a new medicinal product. The vast majority of existing papers analysed the gains of risk-sharing schemes in terms of prices, expected profit for the pharmaceutical company and number of patients treated, with the aim to design the optimal risk-sharing agreement. The impact of the economic analysis of such schemes is ambiguous as it mainly depends on various parameters such as the level of the risk adversity of the pharmaceutical company and the health insurer, the degree of illness of patients, the level of the monitoring costs and the listing process.

The following modeling parts, will analyse how such schemes can alleviate risk related to uncertainty on the real effectiveness of new medicinal products by introducing some asymmetries which exist in health markets and have been addressed in the first chapter: firstly innovation incentives (moral hazard, also-called hidden action), secondly asymmetric information focused on demand (adverse selection, also-called hidden information). Antonanzas (2013, p. 361) stressed that risk-sharing agreements might be considered as "a way of controlling costs" which are "not deemed very useful for dealing with uncertainty and information asymmetries". The aim is to analyse how risk-sharing schemes can be a means to solve

these asymmetric information issues and to allow patients earlier access to innovative medicinal products while managing health care budgets. To that purpose, in the following parts, the focus of the analysis will be shifted from the trade-off of sharing the risks between the health insurer and the pharmaceutical company to the efficiency incentives in the presence of uncertainty brought by such agreements.

4.2 Risk-sharing schemes as a means of improving innovation incentives in the presence of hidden action

In this section, once the moral hazard issues (also called a hidden action) related to pharmaceutical firms' incentives to innovate have been reviewed (4.2.1), the model's general assumptions, with regard to the utility of the health insurer and the pharmaceutical firm's profits will be presented (4.2.2). The model will then take into account an example where the information is symmetrically distributed (4.2.3) and asymmetrically distributed (4.2.4) in order to compare the impact of risk-sharing schemes in both cases and conclude on the results (4.2.5).

4.2.1 Motivation and aim

While the impact of risk-sharing schemes on pharmaceutical companies' incentives to continuously innovate in the presence of information asymmetries has not been analysed in depth so far in the economic literature (4.2.1.1), a principal-agent model taking into account the distribution of the information is proposed in order to analyse the impact of such schemes on innovation incentives (4.2.1.2).

4.2.1.1 Review of existing literature on risk-sharing schemes and innovation incentives

Lilico and Barros investigated how risk-sharing schemes can improve innovation incentives. They argued that pharmaceutical companies can have an influence on their own knowledge of the product and, by investing in R&D, might also increase the product's probability of success. Pharmaceutical firms might, for example, find that the product is less effective in conjunction with other treatments, or vice versa. Lilico's (2003) and Barros' (2011) papers addressed the issue of the extent to which performance-based risk-sharing schemes can improve pharmaceutical companies' incentives to continuously innovate and increase their product's probability of success. Contrary to Antonanzas et al. who in their paper modeled the uncertainty with a random variable representing the probability of a cure, Lilico and Barros analysed the impact of a risk-sharing scheme on the pharmaceutical company's incentives to innovate in the quality of their product. The focus of the following analysis will be shifted from the risk-sharing part to the incentives effects brought by these agreements.

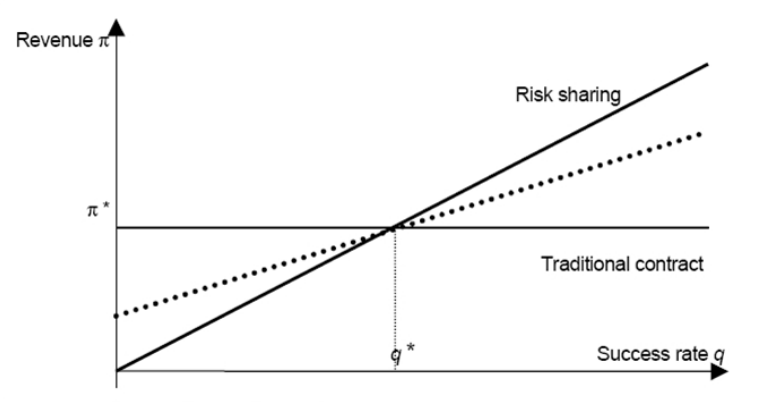
Lilico (2003) Lilico (2003) analysed in his benchmark model risk-sharing schemes in a framework of n identical patients, where pharmaceutical companies compete to treat patients.

Lilico mentioned the impact of risk-sharing schemes on pharmaceutical companies' incentives to innovate in an extension, and investigated the direct link between efficacy and financial returns. He noted

that, under a performance-based risk-sharing scheme, pharmaceutical company's profits are based on the real success rate of the medicine. Hence, by granting a higher price when the product is successful, such agreements increase the pharmaceutical companies' incentives to continuously invest in R&D for their product and therefore further increase their knowledge on the product and its success (modification of chemical component, better monitoring). The higher the success rate of their product, the higher the profits for the pharmaceutical company under a risk-sharing scheme. Consequently, Lilico explained that pharmaceutical firms would exploit any improvement in the success rate of their medicinal product, even after marketing.

Lilico presented his economic argumentation but left out a theoretical explanation by providing a graphical illustration (cf. figure 4.2). The model at hand contributes to the literature and additionally shows the design of an optimal (second best) contract menu.

Figure 4.2: Incentives to innovate: Normal price-setting and risk-sharing scheme



Sources: Lilico, 2003.

His illustration, which depicts a normal price setting and a risk-sharing agreement, shows by representing the revenue on the vertical axis and the success rate on the horizontal axis that, under normal price setting, the revenue does not depend on the realisation of the medicinal product's success rate but on the expected one which is fixed. By comparison, a risk-sharing scheme makes the revenue depend on the actual success rate of the medicinal product. For this reason, the pharmaceutical company has incentives to invest, in order to increase the actual success rate and to have higher than expected profits.

Barros (2011) Barros (2011) also analysed in an extension of his paper how a risk-sharing agreement might change pharmaceutical companies' incentives to innovate. By assuming that the price is fixed and that the production costs are equal to zero, Barros explained how the implementation of a risk-sharing scheme might change the pharmaceutical company's incentives to invest in quality. This implies a better distribution of the medicinal product's probabilities for success. However, the implementation of a risk-

sharing scheme might also induce less investment as the company might expect less benefit per treatment provided. Barros concluded that the impact of a risk-sharing scheme depends on the costs of verifying whether the product was successful or not, and on the number of patients treated. For this reason, the result is ambiguous and such schemes cannot be considered per se as an instrument to promote innovation.

4.2.1.2 Contribution to the theoretical literature on risk-sharing schemes

The objective of this section is to focus on the issue of how risk-sharing schemes can solve the moral hazard issues which arise around the innovation efforts of pharmaceutical companies and contribute in promoting R&D incentives.

Firms lack incentives to undertake R&D as the price of the medicinal product depends on its efficacy as assessed during clinical trials and not on the ex-post effectiveness of the product as assessed during real conditions of use. This situation may best be illustrated by the principal/agent theory (Laffont and Martimort, chap. 4). The principal- the health insurer- wants to sign a contract with the agent- the pharmaceutical company- for the delivery of an innovative medicinal product which is characterised by its efficiency to treat the patient. However, the health insurer does not know the extent to which the pharmaceutical company is willing to provide an efficient product and to keep investing in increasing its success over the time. Indeed, a price is set after the medicinal product is granted its marketing authorisation based on the efficacy assessed in clinical trials (expected or ex-ante effectiveness). The price remains the same, whether the patient is healed after the treatment or not. As a result, since the price remains unchanged whether the product is successful or not, the pharmaceutical company does not have any incentive to improve its knowledge on the product and the probability of success following treatment. This is typically a case of moral hazard (hidden action).

To solve the moral hazard issue, the agent will be involved in the risk of the product not being successful. Hence, the implementation of a performance-based risk-sharing scheme which links the price paid by the health insurer to the pharmaceutical company can offer firms incentives to invest in R&D for their product, thus increasing the probability of successful treatment. In the following example, for simplicity reasons, the terms expected success to represent the ex-ante effectiveness and real success for the ex-post effectiveness will be used.

While Lilico only gave an intuitive graphical representation of the impact of a risk-sharing scheme on the incentives to innovate and concluded that it has a positive impact, Barros chose to introduce more variables and found an ambiguous impact. Both authors addressed the information asymmetries on the expected success and the real success of the medicinal product, which is at the basis of the implementation of a risk-sharing scheme. However, neither differentiated between symmetric or asymmetric information.

The underlying intention is that the impact of a risk-sharing scheme varies, whether the information is symmetric or asymmetric.

The model proposed differs from the framework of Antonanzas et al. (2011) in three main points. First of all, it is a principal/agent model. Hence, if the principal wants the agent to deliver a product of a higher efficacy, he needs to pay a higher price. Secondly, Antonanzas et al. assume symmetric information while the following model will be looking at asymmetric information issues. Finally, the model proposed assumes risk neutral agents.

Such a modeling approach with a principal-agent framework with risk-neutral agents was followed in the last version of Antonanzas (2013). In this version, Antonanzas assumes that the principal, the health insurer, proposes the type of contract it will offer to the pharmaceutical company based on the results in terms of efficacy of the clinical trials performed. Depending on the characteristics of the patients and their responsiveness to the medicinal product, the pharmaceutical company decides on the size of the market it will serve. Antonanzas concludes that when the health insurer takes its pricing and reimbursement decision based on cost-effectiveness considerations, it will always propose the pharmaceutical company a risk-sharing scheme. The following model departs from Antonanzas' analysis (2013) as it takes into account the existing information asymmetries in pharmaceutical markets (i.e. moral hazard issues) and considers incentives for innovation. The aim is to show that the results of Antonanzas (2011, 2013) are still valid with asymmetric information. In terms of incentives for innovation, the model also shows that due to the incentives effects, risk-sharing schemes can in certain cases be used to promote continuous innovations in drugs.

The investigation of the impact of such agreements on innovation incentives is important in light of the growing trend towards risk-sharing schemes and the issues surrounding innovation in pharmaceutical markets. The following model will further complement Lilico's analysis by demonstrating his thesis and showing when it is profitable for a firm to invest in increasing the success rate of its medicinal product in relation to the costs incurred, as well as developing Barros's thesis by distinguishing two cases, whether the information is symmetrically or asymmetrically distributed.

Once the situation has been analysed, in the absence of a risk-sharing scheme, subsequent model considers two cases where a risk-sharing scheme is in place, whether the innovation efforts of the pharmaceutical company can be observed by the health insurer (symmetric information) or not (asymmetric information). Then, having calculated the corresponding prices with the implementation of a performance-based risk-sharing scheme, the comparison from the point of view of the utility of the health insurer is made, whether and when it is profitable for the health insurer to promote innovation and assess the impact on social welfare. Due to the fact that the focus of the following analysis is shifted towards the investigation

of the impact of risk-sharing schemes in the presence of information asymmetries, following models will assume that the principal (i.e. the health insurer) is risk-neutral.

4.2.2 General assumptions

Reimbursement process and success rate Assuming that a pharmaceutical company produces an innovative medicinal product to treat a specific disease with a marginal constant cost c, $c > 0$. The health insurer, acting as the final payer, decides whether to reimburse the medicinal product or not. If the product is reimbursed, it is prescribed to the patient by a physician and the health insurer pays a price p to the pharmaceutical company. If the product is not reimbursed, it is assumed for simplicity reasons, that the product is not prescribed to the patient and the health insurer does not have to pay the pharmaceutical company.

The health insurer's reimbursement decision depends on the medicinal product's probability of success q_i. It is assumed that the product is effective to heal the disease with a probability q_0, $q_0 \in [0; 1]$, across a population of n patients[16]. Let the utility of the patients be measured by their health status w. The patient's utility increases when the disease is being cured and decreases when this is not the case. It is assumed that the disease causes the patient a disutility d, $d > 0$. As with Barros and Lilico, it is assumed that the fixed costs are sunk.

In accordance with Lilico (2003) and Barros (2011), it is also assumed that the medicinal product's probability of success, namely q, can be improved by the pharmaceutical company, as it can choose to invest in R&D and increase its product's probability of success. If q_0 is the initial probability of success for the treatment, q_1 represents the new probability of success after the firm has invested in R&D. It is assumed that $q_1 > q_0$.

Utility function of the health insurer The health insurer, which for simplicity reasons is risk-neutral, maximises its utility U while taking into account the medicine's costs and the patient's health. Let U be the utility function of the health insurer in case the product is reimbursed and U^{NT} if the health insurer decides not to reimburse the medicinal product.

- If the product is reimbursed

The utility function of the health insurer where the product is reimbursed and no innovation has been performed can be written as:

[16] Lilico (2003) assumes in his model that being treated leads to a certain disutility (given by the term T in his model) due to the unpleasantness of the treatment or the risk that the treatment does not work but he does not assume any disutility from not being treated. In the following model, this assumption is left and it is assumed that the utility of the patients can be measured by their health status w.

$U^0 = n(w-p)q_0 + n(w-p-d)(1-q_0)$. If the pharmaceutical company has invested in increasing the success rate of its product from q_0 to q_1, the utility of the health insurer can be rewritten as:

$U^1 = n(w-p)q_1 + n(w-p-d)(1-q_1)$.

- If the product is not reimbursed

If the health insurer does not reimburse the product, the patient is not treated and the utility function of the health insurer can be written as:

$U^{NT} = n(w-d)$.

This assumption can be explained by the physicians' prescription behaviour who act as an agent of their patient and would not prescribe a non-reimbursed product which would be expensive for their patient.

Profit function of the pharmaceutical company The profit of the pharmaceutical company (Π) is equal to:

$\Pi = n(p-c)$ if the patient is treated,

and if the patient is not treated, the profits are equal to:

$\Pi_{NT} = 0$. If the product is not reimbursed, the product is not prescribed and the pharmaceutical company cannot sell its product, thus it does not make a profit.

This setting corresponds to the usual price-setting when no risk-sharing scheme is in place. It is assumed in the following analysis that it is for the health insurer always worth reimbursing the medicinal product, as $dq_0 > c$. The aim, therefore, is to analyse cases with risk-sharing schemes in order to assess the impact of implementing such schemes when the information is symmetrically and asymmetrically distributed. For the sake of clarity, the number of patients treated n is normalised to 1.

4.2.3 Modeling with symmetric information

Firstly symmetric information will be analysed where, in the handling of the contract, the health insurer can verify the efforts made by the pharmaceutical company. Then, the situation without risk-sharing will be analysed (4.2.3.1) followed by with risk-sharing (4.2.3.2) to compare both situations and draw an intermediate conclusion on the relevance of a risk-sharing scheme where symmetric information offers firms incentives to innovate (4.2.3.3).

4.2.3.1 Without risk-sharing scheme

The health insurer can observe whether the pharmaceutical firm has innovated or not. Examples where the company has not innovated (a) and where it has innovated (b) will be differentiated.

a. If the pharmaceutical company does not innovate The health insurer's incentives to promote innovation when no risk-sharing scheme is in place are now analysed. Without a risk-sharing scheme, the health insurance maximises its utility by taking into account the pharmaceutical company's participation constraints, meaning that both the price and the company´s profits will be positive. The health insurer's maximisation programme can be expressed as:

$\max_p q_0(w-p) + (1-q_0)(w-p-d) = (w-p) - (1-q_0)d$

s.t. $p \geq 0$ and $(p-c) \geq 0$

Hence, the profitable price is given by $p = c$.

b. If the pharmaceutical company innovates The pharmaceutical company can choose to innovate and by doing so it will incur some (fixed) R&D costs which are equal to ψ. The health insurer's maximisation problem which takes into account the pharmaceutical company's participation constraints, in this case consists of:

$\max_p q_1(w-p) + (1-q_1)(w-p-d)$

s.t. $p \geq 0$ and $(p-c) - \psi \geq 0$

The expression of p found is equal to:

$p = c + \psi$.

Calculation of the utility of the health insurer

- Where there is no innovation

The utility of the health insurance, when the pharmaceutical firm does not innovate, U^0, is given by:

$U^0 = q_0(w-p) + (1-q_0)(w-p-d) = (w-p) - (1-q_0)d$

In case of the utility maximising price p, $p = c$, and the utility level of the health insurance can be written as

$U^0 = (w-c) - (1-q_0)d$

- Where there is innovation

Now calculating U^1 when the firm innovates, it is given by $U^1 = q_1(w-p) + (1-q_1)(w-p-d) = (w-p) - (1-q_1)d$,

and by replacing the value of p, then $p = c + \psi$, so that:

$U^1 = (w - c - \psi) - (1 - q_1)d$

Thus comparing both utilities, $U^1 \geq U^0 \iff (w - c - \psi) - (1 - q_1)d \geq (w - c) - (1 - q_0)d$

$\iff -\psi + d(q_1 - q_0) \geq 0$

$\iff \psi \leq d\Delta q$ or $d \geq \frac{\psi}{\Delta q}$ with $\Delta q = q_1 - q_0$

Only when the innovation costs are low enough($\psi \leq d\Delta q$) or the disutility caused by the disease large enough ($d \geq \frac{\psi}{\Delta q}$) , will the utility of the health insurer be higher if the firm innovates, than if it does not innovate.

Calculation of the social welfare Social welfare is now calculated in both cases.

- Where there is no innovation

If there is no innovation, the social welfare SW^0 is equal to:

$SW^0 = U^0 + \Pi^0 = (w - p) - (1 - q_0)d + (p - c)$

$\iff (w - c) - (1 - q_0)d + (c - c) = w - c - (1 - q_0)d)$

- Where there is innovation

If the pharmaceutical firm invests in R&D to increase its product's probability of success, the social welfare is equal to:

$SW^1 = U^1 + \Pi^1 = (w - p) - (1 - q_1)d + (p - c) - \psi$

$\iff SW^1 = (w - c - \psi) - (1 - q_1)d + (c + \psi - c) - \psi$

$\iff SW^1 = (w - c - (1 - q_1)d) - \psi$

Comparing the social welfare in both cases,

$SW^1 \geq SW^0 \iff w - c - (1 - q_1)d - \psi \geq w - c - (1 - q_0)d$

$\iff \psi \leq d\Delta q$

which is the same condition that was previously found for the utility of the health insurer.

The comparison showed that only when the costs of innovation are lower than $d\Delta q$, then innovation leads to an increase in both the utility of the health insurer and the social welfare. The fact that innovation leads to increase the utility of the health insurance and the social welfare depends on two variables, d and Δq. On the one hand, the higher the disutility brought by the disease, and on the other hand the higher the expected success rate of the medicinal product. The variable c representing the marginal costs does not have any role.

4.2.3.2 Incorporating a risk-sharing scheme

A performance-based risk-sharing scheme is now assumed. The introduction of a performance-based risk-sharing scheme leads to the assumption that if the product is efficient, then the health insurer will pay a price $\bar{p}$ to the pharmaceutical company, and if the product is not efficient, the price paid to the pharmaceutical company will be equal to $\underline{p}$, $\underline{p} \leq \bar{p}$.

a. When the pharmaceutical company does not innovate In cases where the pharmaceutical company does not innovate, the probability of success for the medicinal product remains q_0. This can be observed by the health insurer, as the information is considered as symmetric.

With the introduction of a performance-based risk-sharing scheme, the utility of the health insurer and the pharmaceutical company's profits can be written respectively as:

$U^{PRS0} = q_0(w - \bar{p}) + (1 - q_0)(w - \underline{p} - d)$ and $\Pi^{PRS0} = \bar{p}q_0 + (1 - q_0)\underline{p} - c$

The health insurer's maximisation problem, which integrates the pharmaceutical company's participation constraint consists of:

$\underset{\underline{p},\bar{p}}{max}\ q_0(w - \bar{p}) + (1 - q_0)(w - \underline{p} - d)$

s.t. $\bar{p}q_0 + (1 - q_0)\underline{p} - c \geq 0$

The Lagrangian equation can be expressed as:

$L = \{q_0(w - \bar{p}) + (1 - q_0)(w - \underline{p} - d)\} + \mu(q_0\bar{p} + (1 - q_0)\underline{p} - c)$

Solving it by using the Kuhn-Tucker conditions, the first-order conditions are:

$-q_0 + \mu q_0 = 0$ (1) and

$-(1 - q_0) + \mu(1 - q_0) = 0$ (2)

From (1) and (2), it follows that the Lagrange multiplier equals one, that is, the participation constraint is binding, $\mu = 1 > 0$. The participation constraint is binding corresponds to $q_0\bar{p} + (1 - q_0)\underline{p} = c$ $\iff \bar{p} = \frac{c}{q_0} - \frac{(1-q_0)}{q_0}\underline{p}$ or $\underline{p} = \frac{c}{1-q_0} - \frac{q_0}{1-q_0}\bar{p}$

Valid couples of $(\underline{p}; \bar{p})$ are, for example, either $(0, \frac{c}{q_0})$ if prices have to be positive/non-negative or, (c, c) as in the case where a risk-sharing scheme does not exist.

b. When the pharmaceutical firm innovates When the pharmaceutical company invests in R&D, the pharmaceutical company's probability of success p increases from q_0 to q_1. The respective utility function of the health insurer and the pharmaceutical company's profits following the implementation of a risk-sharing scheme can be written as:

$U^{PRS1} = q_1(w - \bar{p}) + (1 - q_1)(w - \underline{p} - d)$ and $\Pi^{PRS1} = \bar{p}q_1 + \underline{p}(1 - q_1) - c - \psi$ with ψ the R&D costs borne by the pharmaceutical company.

The maximisation problem integrating the participation constraint of the pharmaceutical company consists of:

$\underset{\underline{p},\bar{p}}{max}\ q_1(w-\bar{p})+(1-q_1)(w-\underline{p}-d)$

s.t. $(\bar{p}q_1+(1-q_1)\underline{p}-c-\psi\geq 0,\ \underline{p}\geq 0,\ \bar{p}\geq 0.$

The Lagrangian equation can be written as:

$L=\left\{q_1(w-\bar{p})+(1-q_1)(w-\underline{p}-d)\right\}+\mu(q_1\bar{p}+(1-q_1)\underline{p}-c-\psi)$

Solving it by using the Kuhn-Tucker conditions, the first-order conditions are:

$-q_1+\mu q_1=0$ and

$-(1-q_1)+\mu(1-q_1)=0$ so that $\mu=1>0$

The participation constraint is binding so that:

$q_1\bar{p}+(1-q_1)\underline{p}=c+\psi \iff q_1\bar{p}+(1-q_1)\underline{p}=c+\psi.$

In the case where $\underline{p}=\bar{p}\iff \underline{p}=\bar{p}=c+\psi$

As $\underline{p}=\bar{p}=c+\psi$, the R&D costs ψ are part of the expression of the price. This result shows that, when innovation can be observed, the health insurer participates in the costs of innovation. The same result was observed in the symmetric case when the pharmaceutical innovates.

Comparison of the utility of the health insurer and the social welfare Having calculated prices in both cases, the utility of the health insurer in both situations is calculated. For these calculations, the symmetric combinations found are chosen as the information is symmetrically distributed. However, all combinations given by the above-mentioned equations are valid and lead to the same results.

- If there is no innovation

The utility of the health insurer in cases where innovation does not take place can be written as:

$U^{PRS0}=q_0(w-\bar{p})+(1-q_0)(w-\underline{p}-d)=q_0(w-c)+(1-q_0)(w-c-d)=(w-c)-d(1-q_0)$

- If innovation is present

Where innovation takes place, the utility of the health insurer is equal to:

$U^{PRS1}=q_1(w-\bar{p})+(1-q_1)(w-\underline{p}-d)=q_1(w-c-\psi)+(1-q_1)(w-c-\psi-d)$

In both cases as well as for the calculation of the social welfare, the same result is found as where a risk-sharing scheme is not implemented.

4.2.3.3 Intermediate conclusion on cases exhibiting symmetric information

Due to the assumed risk neutrality of the agents, the model's results show that in cases where the information is symmetrically distributed, there is little use in implementing a risk-sharing scheme to

provide firms with incentives to innovate. The same results concerning the utility of the health insurer and the social welfare are found in cases demonstrating typical price-setting and risk-sharing schemes.

4.2.4 Modeling with asymmetric information

The same model assumptions apply as in the example of symmetric information. The difference with the previous example lies in the fact that in the asymmetric case the health insurer cannot observe the efforts made by the pharmaceutical company to increase the medicinal product's probability of success. First, a non risk-sharing scheme will be analysed (4.2.4.1) and then the implementation of a risk-sharing scheme (4.2.4.2) before drawing a conclusion as to the use of a risk-sharing scheme to promote incentives to innovate when the information is asymmetrically distributed (4.2.4.3).

4.2.4.1 Without risk-sharing scheme

The health insurer cannot observe the efforts made by the pharmaceutical company. In a normal price setting, the health insurer cannot request this information. Therefore, in addition to the participation constraint which was binding in the example with symmetric information, an incentive constraint for the pharmaceutical company is also fulfilled, meaning that the pharmaceutical company's profits are higher in cases where innovation is present than when it is not.

As the R&D costs ψ are not negative, the incentive constraint mentioned is never satisfied and thus the firm will never innovate. One possible solution is hence $p = c$, which is the same solution as in the example of symmetric information where no innovation is taking place.

The result shows that when the information is asymmetric, the pharmaceutical firm would never innovate in the absence of an incentive.

4.2.4.2 Incorporating a risk-sharing scheme

The effort made by the pharmaceutical company cannot be observed by the health insurer. Therefore, an incentive constraint should be applied by the health insurer in order to make the pharmaceutical company choose the right option. This distinction applies whether the health insurer wants to promote innovation or not.

a. The health insurer wants to promote innovation In the maximisation of its utility, the health insurer must consider the pharmaceutical company's participation constraint (P) whiche PASh is equal to $\bar{p}q_1 + (1 - q_1)\underline{p} - c - \psi \geq 0$, as well as its incentive compatibility constraint as the information

is asymmetrically distributed (IC), which is equal to $q_1\bar{p} + (1-q_1)\underline{p} - c - \psi \geq q_0\bar{p} + (1-q_0)\underline{p} - c \Longleftrightarrow$ $\Delta q(\bar{p} - \underline{p}) - \psi \geq 0$. The limited liability constraint, $\underline{p} \geq 0$ and $\bar{p} \geq 0$, is denoted by (LL).

The maximisation problem including the participation, incentive compatibility and limited liability constraints consists of:

$\underset{\underline{p},\bar{p}}{max}\ q_1(w-\bar{p}) + (1-q_1)(w-\underline{p}-d)$

s.t. (IC), (PP) and (LL)[17]

$L = \{q_1(w-\bar{p}) + (1-q_1)(w-\underline{p}-d)\} + \mu(\Delta q(\bar{p}-\underline{p}) - \psi) + \lambda(q_1\bar{p} + (1-q_1)\underline{p} - c - \psi) + \nu\bar{p} + \zeta\underline{p}$

Solving the optimisation problem using the Kuhn-Tucker conditions, the first-order conditions are:

$-q_1 + \mu\Delta q + \lambda q_1 + \nu = 0$ (1) and

$-(1-q_1) - \mu\Delta q + \lambda(1-q_1) + \zeta = 0$ (2)

By adding up (1) and (2), then $-1 + \lambda + \nu + \zeta = 0$

due to (IC), $\bar{p} > 0 \Rightarrow \nu = 0 \Rightarrow \lambda + \zeta = 1$

- Case 1: $\frac{c+\psi}{q_1} \geq \frac{\psi}{\Delta q} \Longleftrightarrow c \geq \frac{q_0}{\Delta q}\psi$

When $c \geq \frac{q_0}{\Delta q}\psi$, the price combination $\underline{p} = 0$ and $\bar{p} = \frac{c+\psi}{q_1}$ constitutes a solution. These values of $\underline{p}$ and $\bar{p}$ fulfil both (P) and (IC):

(P) $q_1\bar{p} + (1-q_1)0 - c - \psi = 0$ and (IC) $\Delta q(\frac{c+\psi}{q_1} - 0) \geq \psi \Longleftrightarrow \frac{c+\psi}{q_1} \geq \frac{\psi}{\Delta q}$

For $\lambda = 1$, $\mu = \nu = \zeta$, all the Kuhn-Tucker conditions are fulfiled. Hence, $\underline{p} = 0$ and $\bar{p} = \frac{c+\psi}{q_1}$ is a solution.

- Case 2: $\frac{c+\psi}{q_1} \leq \frac{\psi}{\Delta q} \Longleftrightarrow c \leq \frac{q_0}{\Delta q}\psi$

In the context of the pharmaceutical industry, where the production costs c are low compared to the costs of innovation ψ, this is a logical assumption. When $\frac{c+\psi}{q_1} \leq \frac{\psi}{\Delta q} \Longleftrightarrow c \leq \frac{q_0}{\Delta q}\psi$, the combination $\underline{p} = 0$ and $\bar{p} = \frac{\psi}{\Delta q}$ constitutes the sole solution. $\underline{p} = 0$ and $\bar{p} = \frac{\psi}{\Delta q}$ obviously fulfils (IC) and (LL). This price combination fulfils also (P) when $q_1\bar{p} = q_1\frac{\psi}{\Delta q} \geq c + \psi$, which corresponds to the situation in case 2. Thus,

$\nu = 0$, $\varsigma = 1$, $\lambda = 0$ and $\mu = \frac{q_1}{\Delta q}$ fulfils all the Kuhn-Tucker conditions.

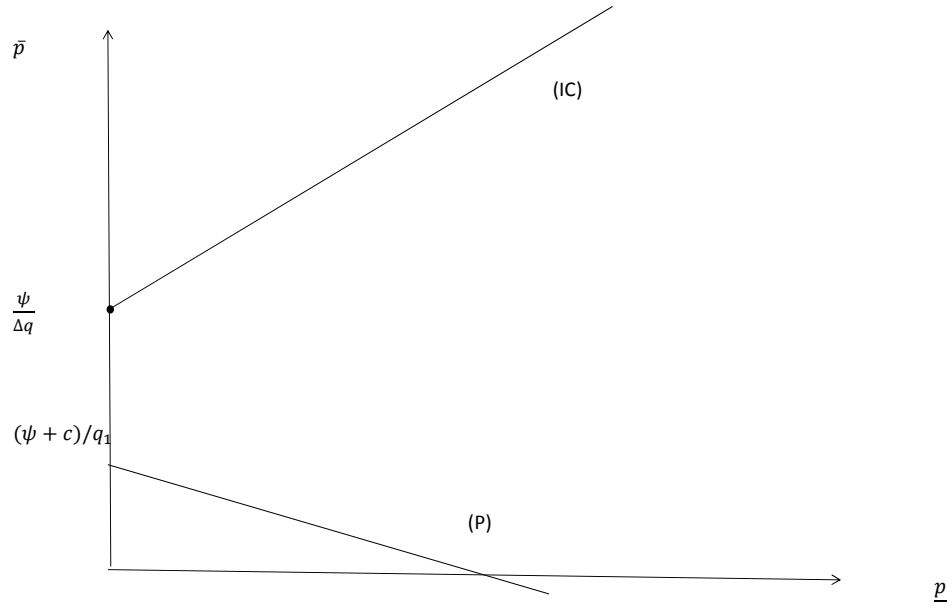
Hence, the price combination $\underline{p} = 0$ and $\bar{p} = \frac{\psi}{\Delta q}$ is a solution which can be observed in figure 4.3.

b. When the health insurer does not want to promote innovation If the health insurer does not want to promote innovation, the maximisation problem, including the participation and the incentives constraints consists of:

$\underset{\underline{p},\bar{p}}{max}\ q_0(w-\bar{p}) + (1-q_0)(w-\underline{p}-d)$

[17] The incentives constraint de facto implies that $\bar{p} \geq \underline{p}$.

Figure 4.3: Graphic representation when the health insurer wants to promote innovation (with $c \leq \frac{q_0\psi}{\Delta q}$)



s.t. $\bar{p}q_0+(1-q_0)\underline{p}-c \geq 0$ (participation constraint, (P)), $q_0\bar{p}+(1-q_0)\underline{p}-c \geq q_1\bar{p}+(1-q_1)\underline{p}-c-\psi \Longleftrightarrow$ $\Delta q(\bar{p}-\underline{p}) \leq \psi$ (incentive constraint, (IC)) and the limited liability constraint (LL), $\bar{p} > 0$ and $\underline{p} > 0$.

The Lagrangian can be written:

$L = \left\{q_0(w-\bar{p}) + (1-q_0)(w-\underline{p}-d)\right\} + \mu(\psi - \Delta q(\bar{p}-\underline{p})) + \lambda(q_0\bar{p} + (1-q_0)\underline{p} - c) + \nu\bar{p} + \zeta\underline{p}$

Solving it by using the Kuhn-Tucker conditions, the first-order conditions are:

$-q_0 + \lambda q_0 - \mu\Delta q + \nu = 0$ (1)

$-(1-q_0) + \lambda(1-q_0) + \mu\Delta q + \zeta = 0$ (2)

By adding up both first-order conditions, then $-1 + \lambda + \nu + \zeta = 0$ (3).

The price combination $\bar{p} = \underline{p} = c$ constitutes a solution. This price combination fulfils (LL) and implies $\nu = \zeta = 0$. It also fulfils:

(P) $cq_0 + (1-q_0)c - c = 0$, and

(IC) $\Delta q(c-c) < \psi$

Hence $\mu = 0$. From (3), it follows that $\lambda = 1$. All the Kuhn-Tucker conditions are fulfiled. The combination $(c;c)$ is only one among others.

The next step is to analyse when the health insurer wants to promote innovation. In the presence of

information asymmetries, when the health insurer does not want to promote innovation, the price set is the same as where there is no risk-sharing scheme. The next step is to analyse when the health insurer wants to promote innovation.

Calculation of the utility of the health insurer

- Where innovation is promoted

The utility of the health insurer is calculated when the innovation will take place and when $c < \frac{q_0\psi}{\Delta q}$ is assumed. The utility of the health insurer can be written as:

$U^{PRS1} = q_1(w - \bar{p}) + (1 - q_1)(w - \underline{p} - d) = -q_1\bar{p} - \underline{p}(1 - q_1) - d(1 - q_1) + w = -q_1\frac{\psi}{\Delta q} - d(1 - q_1) + w$ with $\underline{p} = 0$ and $\bar{p} = \frac{\psi}{\Delta q}$.

- Where no innovation is promoted

The utility of the health insurer if innovation is not promoted can be written as:

$U^{PRS0} = q_0(w - \bar{p}) + (1 - q_0)(w - \underline{p} - d) = w - c - d(1 - q_0)$ with $\bar{p} = \underline{p} = c$

Comparison of the utility levels From the health insurer's point of view, it is profitable to give firms incentives to innovate when:

$U^{PRS1} > U^{PRS0} \iff -q_1\frac{\psi}{\Delta q} - d(1 - q_1) + w > w - c - d(1 - q_0)$ with $\Delta q = q_1 - q_0$

$\iff d > \frac{\psi q_1 - \Delta q c}{(\Delta q)^2} = \frac{\psi q_1}{(\Delta q)^2} - \frac{c}{\Delta q} > 0$, or expressed in another way, $\psi < \frac{\Delta q(c + \Delta q d)}{q_1}$

As a result, the utility of the health insurer is higher by promoting innovation when the losses caused by the disease are bigger than the losses caused by the diverse costs represented by $\frac{\psi q_1}{(\Delta q)^2} - \frac{c}{\Delta q}$ (*) . Or, expressed in another way, when $\psi < \frac{\Delta q(c + \Delta q d)}{q_1}$. Giving firms incentives to innovate is profitable for the health insurer when the damage caused by the disease and the corresponding marginal costs are higher than the proportionally weighted costs of innovation. In this situation only, it is profitable when a risk-sharing scheme is in place.

Assume that the situation corresponds to case 2 where $c \leq \frac{q_0\psi}{\Delta q}$. It is also assumed, if the health insurer wants to promote innovation, that $c < \frac{q_0\psi}{\Delta q} \iff \psi > \frac{c\Delta q}{q_0}$. The health insurer will promote innovation when, $U^{PRS1} > U^{PRS0} \iff \frac{c\Delta q}{q_0} \leq \psi \leq \frac{\Delta q(c + \Delta q d)}{q_1}$.

$\frac{c\Delta q}{q_0} \leq \psi \leq \frac{\Delta q(c + \Delta q d)}{q_1}$

$\iff cq_1 \leq q_0(c + \Delta q d) \iff c \leq q_0 d.$

The condition for the upper limit to be higher than the lower limit is$c \leq q_0 d$. This means that the health insurer would support innovation as long as the pharmaceutical company's costs of production are smaller than the disutility caused by the disease multiplied by the probability of success.

Calculation of the social welfare If the health insurer does not want to give the pharmaceutical firm incentives to innovate, then the social welfare SW^{PRS0} is equal to:

$SW^{PRS0} = U^0 + \Pi^0 = w - c - d(1 - q_0) + q_0 c + (1 - q_0)c - c$

$\iff SW^{PRS0} = w - c - d(1 - q_0)$

The social welfare in cases where the health insurer is willing to give the pharmaceutical firm incentives to innovate is equal to:

$SW^{PRS1} = -q_1 \frac{\psi}{\Delta q} - d(1 - q_1) + w + \frac{\psi}{\Delta q} q_1 - c - \psi$

$\iff SW^{PRS1} = w - d(1 - q_1) - c - \psi$

Comparison of social welfare levels Social welfare is higher when the health insurer chooses to promote innovation since:

$SW^{PRS1} > SW^{PRS0} \iff w - d(1 - q_1) - c - \psi > w - c - d(1 - q_0) \iff \psi < d\Delta q$

It is assumed that $c < \frac{q_0 \psi}{\Delta q}$. Thus, resulting from (*), in the example $\frac{c\Delta q}{q_0} < \psi < d\Delta q \Longrightarrow c < dq_0$, the social welfare will be higher when the health insurer offers the firm incentives to innovate.

4.2.4.3 Intermediate conclusion on cases exhibiting asymmetric information

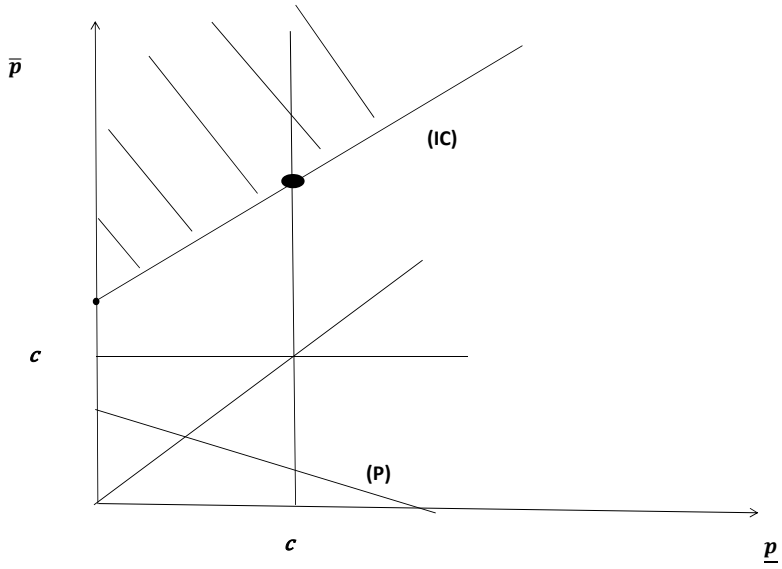
In contrast to examples of symmetric information, the health insurer finds it profitable to incentivise pharmaceutical companies by implementing a risk-sharing scheme. Its decision on whether to provide incentives or not depends on the level of the diverse costs involved. Assuming that $c < \frac{q_0 \psi}{\Delta q}$ the limit $(d\Delta q)$ is larger than $\frac{\Delta q(c + d\Delta q)}{q_1}$ found previously for the utility of the health insurer, there are cases where it would be socially desirable to incentivise innovation, but the health insurer is unlikely to, because the costs are too high. It can be observed from these results that whenever the health insurer provides incentives for innovation, it is always socially desirable.

Relevance of an assumption $\underline{p} \geq c$ and $\bar{p} \geq c$ Assume now, ot of pure interest, that with the limited liability constraint both $\underline{p}$ and $\bar{p}$ are higher than the marginal costs c. In light of the reality of the health care environment, in addition to the investment costs (ψ), the pharmaceutical firm has marginal production costs c.

Analysing what happens if it is assumed that $\bar{p} \geq c$ and $\underline{p} \geq c$, then symmetric information is not relevant as nothing would change, due to the participation constraint. It is assumed that the situation analysed corresponds to the case 2 where $c \leq \frac{q_0 \psi}{\Delta q}$.

The same result is found with asymmetric information, when the health insurer does not want to promote innovation. The assumption does not change anything as the same results as previously are

Figure 4.4: Graphic representation in case 2:



found: $\bar{p} = \underline{p} = c$. Hence, the condition is already fulfilled.

If the health insurer wants to promote innovation, then the prices set should fulfill $q_1(\bar{p}-\underline{p}) = c+\psi-\underline{p}$ with $\bar{p} \geq c$ and $\underline{p} \geq c$. At the equilibrium, (IC) is binding, not (P) so that $\underline{p} = c$ which corresponds to $\bar{p} = c + \frac{\psi}{\Delta q}$. Figure 4.4 provides with a graphical representation of the price combination $(\bar{p}, \underline{p})$.

The utility of the health insurer providing incentives to innovate is equal to:

$U^{PRS1'} = q_1(w - \bar{p}) + (1 - q_1)(w - \underline{p} - d) = q_1(w - c - \frac{\psi}{\Delta q}) + (1 - q_1)(w - c - d)$

$\iff U^{PRS1'} = w - c - d(1 - q_1) - \frac{q_1\psi}{\Delta q}$

The utility of the health insurer not offering incentives to innovate is equal to:

$U^{PRS0'} = q_0(w - \bar{p}) + (1 - q_0)(w - \underline{p} - d) = q_0(w - c) + (1 - q_0)(w - c - d)$

$\iff U^{PRS0'} = w - c - (1 - q_0)d$

It is more profitable for the health insurer to promote innovation in this case, when:

$U^{PRS1'} > U^{PRS0'} \iff w - c - d(1 - q_1) - \frac{q_1\psi}{\Delta q} > w - c - (1 - q_0)d$

After some simplification, $d > \frac{q_1\psi}{\Delta q^2}$ or, expressed in another way, $\psi < \frac{d\Delta q^2}{q_1}$. Previously, $d > \frac{\psi q_1}{\Delta q^2} - \frac{c}{\Delta q}$ and $\psi < \frac{\Delta q(c+\Delta q d)}{q_1}$.

Concerning the social welfare, when innovation is promoted, it is equal to:

$SW^{PRS1'} = U^{PRS1'} + \Pi^{PRS1'} = \left[w - c - d(1 - q_1) - \frac{q_1\psi}{\Delta q}\right] + \left[(\frac{\psi}{q_1} + c)q_1 + (1 - q_1)c - c - \psi\right]$

$\iff SW^{PRS1'} = w - c - d(1 - q_1) - \frac{q_1\psi}{\Delta q}$

When innovation is not promoted, it is equal to:

$SW^{PRS0'} = U^{PRS0'} + \Pi^{PRS0'} = [w - c - (1 - q_0)d] + [cq_0 + (1 - q_0)c - c]$

$\iff SW^{PRS0'} = w - c - d(1 - q_0)$

The social welfare is higher when innovation is promoted in case:

$SW^{PRS1'} > SW^{PRS0'} = w - c - d(1 - q_1) - \frac{q_1\psi}{\Delta q} > w - c - d(1 - q_0)$

$\iff \psi < \frac{d\Delta q^2}{q_1}$

Then, as previously $\psi < d\Delta q$, the assumption with the limited liability constraint that both $\underline{p}$ and $\bar{p}$ are higher than the marginal costs c leads to decrease the threshold for ψ. Assuming a limited liability constraint where the price cannot be less than the marginal costs leads to decrease the threshold where a risk-sharing scheme would be beneficial for the social welfare.

4.2.5 Results

Results of the model show that, under certain conditions, risk-sharing schemes can be used as an instrument to promote innovation incentives. This is not always the case and the implementation of risk-sharing schemes by healthcare authorities also have different reasons.

Consequently, if the information is symmetric - corresponding to a situation where the health insurer can observe the pharmaceutical firm's efforts - same results can be achieved by implementing a risk-sharing scheme as with usual contracts.

However, risk-sharing schemes can be relevant in promoting innovation where asymmetric information is present, meaning a situation where the health insurer cannot observe the pharmaceutical company's innovation efforts when certain conditions about the levels of the R&D costs and the disutility caused by the disease are met. Therefore, the model showed that, in order for the health insurer to be willing to give firms incentives to innovate, R&D costs must be within a certain range, otherwise it is not profitable for the health insurer, though it would have a positive impact on the social wefare. Giving firms incentives to innovate by implementing a risk-sharing scheme depends on the level of costs compared to the disutility caused by the disease and the performance of the drug.

The model contributes to the economic literature on risk-sharing schemes to the extent that it shows when a risk-sharing scheme can be, and above all, should be implemented to promote continuous innovation by pharmaceutical companies on their product. It also stresses, that cases occur where promoting innovation by means of risk-sharing scheme would be socially optimal but health insurers do not implement it as the costs they would have to bear would be too high.

Three main results can be stressed:

1. Innovation can be promoted with the implementation of a risk-sharing scheme.

2. Where R&D costs are low enough and the disutility caused by the disease is high enough, the health insurer will have incentives to promote innovation.

3. Examples exist where it would be beneficial from a social welfare point of view to promote innovation, but not from the health insurer's point of view. However, whenever the health insurer promotes innovation, it is always beneficial from a social welfare point of view.

As a general conclusion, drawn from a comparison of the different examples, risk-sharing schemes are useful to promote innovation and lead to an increase in social welfare when the information is asymmetric. The calculations also demonstrate that innovations cannot be incentivised when no risk-sharing scheme is implemented. However, the level of costs incurred is a key variable in the health insurer's decision of whether to promote innovation or not.

Comparison of these results with empirical studies Hunter et al. (2010) in their literature review mention that risk-sharing schemes are useful to establish evidence of data on the effectiveness of medicinal products while giving incentives to pharmaceutical firms to continuously improve their product. Thus, these results are in line with Adamski's (2010) results, who concluded that a risk-sharing scheme is desirable for innovative medicinal products which treat a high priority disease with important health benefits. This corresponds to the variable d which represents the disutility of the disease. In examples where the disutility is high enough, it was shown that the implementation of a risk-sharing scheme is desirable.

Cook et al. (2008) also empirically found that risk-sharing schemes led to an increase in the product quality by encouraging pharmaceutical manufacturers to market more innovative medicinal products. However, they mentioned two factors which place these results into perspective and mitigate the impact of these schemes on the quality of the product. Performance-based risk-sharing agreements might be undermined by monitoring issues linked to data collection on the success of the product and by the lack of transparency displayed by the different schemes implemented, especially with regard to the pharmaceutical companies' uncertainty on the reimbursement price. These two circumstances weaken the investment incentives in the quality of the product.

4.3 Risk-sharing schemes as a way for pharmaceutical manufacturers to signal the effectiveness of their product in the presence of hidden information

Health insurers' reimbursement decision, as reviewed earlier, is based on the medical added value of a medicinal product, which in turn depends on the R&D efforts undertaken by the pharmaceutical company. As these efforts cannot be observed by the health insurer at the time of the reimbursement decision, a situation of hidden information (also called adverse selection) arises where the pharmaceutical company has an informational advantge over the health insurer. Based on the screening model proposed by Laffont and Martimort, it can be shown that risk-sharing agreements have the potential to provide efficient pharmaceutical companies with incentives to deliver a product of a higher quality (4.3.1). Once the structure and assumptions of a signaling model have been presented, it can be shown that under some specific conditions a separating equilibrium arise where risk-sharing schemes are only offered by pharmaceutical companies producing an effective product (4.3.2). To conclude, policy implications from the models presented are drawn (4.3.3).

4.3.1 Hidden information and screening issues

Once the scarce literature on the impact of risk-sharing schemes on hidden information issues has been briefly reviewed (4.3.1.1), Laffont and Martimort's (2001) proposed screening model is adapted to analyse the extent to which risk-sharing schemes can be considered as instrumental in making pharmaceutical firms deliver products of a higher expected quality than without (4.3.1.2).

4.3.1.1 Presence of hidden information and review of the existing literature

The issue of adverse selection arises when a task is delegated by a principal to an agent who has private information. An adverse selection results from this hidden knowledge about a parameter of the principal's optimisation problem (Laffont and Martimort, chapter 2). Both contract parties hence do not have the same information available prior to contracting for a product of a given quality as the principal cannot observe the costs of the agent. In the specific case of pharmaceuticals, the health insurer delegates to a pharmaceutical company the task to manufacture a medicinal product. The price of the product depends on medical added value of the product which in turn depends on the R&D efforts. The health insurer does not know the costs of the pharmaceutical company in terms of R&D and related costs given the quality of the product.

In the presence of this information gap, the principal is before contracting and setting a medicinal product in the list of reimbursed products in a disadvantageous situation. Due to this informational issue, the first-best solution cannot be achieved due to the strategic behaviour of the agent.

Hence, in the presence of hidden information the issue is less on the action to take after contracting than designing the type of contract that the agent is ready to accept and which makes them disclose their private information in order to decrease their informational advantage. This informational constraint is also at stake as the health insurer can either decide to reimburse the medicinal product at unit price or not, or choose other types of contracts to make the pharmaceutical company reveal their private information.

While empirical articles (Cook et al. 2008, Towse et al. 2010) mention the role of risk-sharing schemes in solving hidden information issues in pharmaceutical markets, theoretical literature is scarce. Cook et al. (2008) and Towse (2010) et al. explain, that the health insurer's perception of costly innovative drugs puts pressure on pharmaceutical companies to build confidence in their product being worth the additional reimbursement expenditure. Consequently, one approach employed to build this confidence and maintain investment incentives is for pharmaceutical companies to enter into a risk-sharing scheme.

4.3.1.2 Application of the Laffont and Martimort's model to hidden information issues in pharmaceutical markets

In the following example, Laffont and Martimort's (2001, pp. 37) screening model is adapted in order to show the extent to which a risk-sharing scheme can provide pharmaceutical firms with incentives to deliver a medicinal product of an expected higher quality. In the following screening model, it is assumed that the health insurer proposes the risk-sharing scheme to the pharmaceutical company to make it reveal their private information.

Modeling Consider a health insurer (hereinafter, the principal) who wants to delegate to a pharmaceutical firm (hereinafter, the agent), the production of a drug of quality q. The term q corresponds to the success rate of the product in treating the patient. The value for the principal of these q units is $S(q)$ with S as a concave function. The marginal value of the product's quality is assumed to be positive and strictly decreasing with the quality.

The pharmaceutical company's production costs are not observable by the principal. However, it is common knowledge that the marginal costs θ belong to the set $\Theta = \left\{\underline{\theta}; \bar{\theta}\right\}$. The agent can be efficient in obtaining a certain quality to treat the patient ($\underline{\theta}$) or inefficient ($\bar{\theta}$). This assumption means that the agent's costs to achieve a certain success rate will be higher if the firm is inefficient. The costs function can be written:

$C(q, \underline{\theta}) = \underline{\theta} q$ with probability v, and

$C(q, \bar{\theta}) = \bar{\theta} q$ with probability $(1 - v)$

The spread of the technological quality on the agent's marginal costs is denoted by $\Delta\theta = \bar{\theta} - \underline{\theta} > 0$. When making its decision on the product's quality, the pharmaceutical company is informed about its type θ. The information structure is assumed to be exogeneous to those involved.

The economic variables considered are q, and p which is the cost of treating with the product, per patient. These variables are both observable and verifiable by a third party.

While Laffont and Martimort describe and derive the first-best and its implementation, the aim of this model is to show the extent to which risk-sharing schemes can be considered instrumental in making the agent increase the quality of the product it supplies. Consequently, the second-best if the marginal cost θ is company's private information, will be directly derived. In this specific case, the principal will give the $\underline{\theta}$ agent incentives to deliver a product of a good quality rather than to mimic the $\bar{\theta}$ firm. Therefore, the allocation must fulfill the following incentive compatibility constraints:

$\underline{p} - \underline{\theta}\underline{q} \geq \bar{p} - \underline{\theta}\bar{q}$ (IC1) and $\bar{p} - \bar{\theta}\bar{q} \geq \underline{p} - \bar{\theta}\underline{q}$ (IC2), as well as the following participation constraints

$\underline{p} - \underline{\theta}\underline{q} \geq 0$ (P1) and $\bar{p} - \bar{\theta}\bar{q} \geq 0$ (P2).

Incentives and participation constraints define the set of incentives' compatible allocations. Incentive compatibility alone implies that the quality level requested by the principal from a $\bar{\theta}$ agent cannot be higher than the quality required from a $\underline{\theta}$ agent, hence $\underline{q} \geq \bar{q}$ (monotony condition).

Information rents Under incomplete information, the $\underline{\theta}$ agent benefits from an information rent which arises out of its ability to mimic the less efficient type. This information rent is due to the pharmaceutical company's informational advantage on its abilities over the health insurer. By mimicking the $\bar{\theta}$-agent, the $\underline{\theta}$-agent would get $\bar{p} - \underline{\theta}\bar{q} = \bar{p} - \bar{\theta}\bar{q} + \Delta\theta\bar{q} = \bar{U} + \Delta\theta\bar{q}$. As a consequence, if the health insurer wants a product with a quality $\bar{q} > 0$, it must offer a positive rent to the $\underline{\theta}$ agent. In respect of the $\bar{\theta}$ agent's utility level, this can be reduced to its lowest level, $\bar{U} = \bar{p} - \bar{\theta}\bar{q} = 0$.

The maximisation function of the principal can be written as:

$\underset{\{(\bar{p},\bar{q});(\underline{p},\underline{q})\}}{max} v(S(\underline{q}) - \underline{p}) + (1 - v)(S(\bar{q}) - \bar{p})$ subject to IC1, IC2, P1 and P2.

By using the definition of the information rents, $\underline{U} = \underline{p} - \underline{\theta}\underline{q}$ and $\bar{U} = \bar{p} - \bar{\theta}\bar{q}$, their expressions can be replaced in the maximisation function and the constraints. Consequently, the new optimisation variables are $\{(\underline{U}, \underline{q}); (\bar{U}, \bar{q})\}$and the maximisation problem of the principal is :

$\underset{\{(\bar{U},\bar{q});(\underline{U},\underline{q})\}}{max} v(S(\underline{q}) - \underline{\theta}\underline{q}) + (1 - v)(S(\bar{q}) - \bar{\theta}\bar{q}) - (v\underline{U} + (1 - v)\bar{U})$

subject to $\underline{U} \geq \bar{U} + \Delta\theta\bar{q}$ (IC 1'),

$\bar{U} \geq \underline{U} - \Delta\theta\underline{q}$ (IC 2'),

$\underline{U} \geq 0$ (P 1'), and

$\bar{U} \geq 0$ (P 2').

Solving the maximisation problem in accordance with Laffont and Martimort, by simplifying the number of relevant constraints, the remaining constraints are IC1' and P2', which must be binding at the optimum of the health insurer's maximisation problem. By substituting them in the health insurer's maximisation problem, a reduced programme is obtained:

$$\underset{\{(\underline{q},\bar{q})\}}{max}\ v(S(\underline{q}) - \underline{\theta q}) + (1-v)(S(\bar{q}) - \bar{\theta}\bar{q}) - v\Delta\theta\bar{q}$$

Solving the maximisation problem results in the quality offered by the efficient type corresponding to the first-best, $\underline{q}^{SB} = \underline{q}^*$, with SB denoting "second-best". However, the quality offered by the least efficient type is lower than the first best, as $\bar{q}^{SB} < \bar{q}^*$. The efficient type receives a positive efficient rent equal to $\underline{U}^{SB} = \Delta\theta\bar{q}^{SB}$ while the less efficient one does not receive anything. Respective second-best prices for the efficient and inefficient types are equal to $\underline{p}^{SB} = \underline{\theta q}^* + \Delta\theta\bar{q}^{SB}$ and $\bar{p}^{SB} = \bar{\theta}\bar{q}^{SB}$.

This analysis in terms of screening complements the previous principal-agent model with hidden action concerning the incentives of the firms to deliver a product of higher quality. While the previous model emphasized the importance of the level of the R&D costs and the disutility caused by the disease in the choice of the health insurer to promote innovation, the conclusions of the screening model highlight the role played by the rent .

The model shows that, when the costs of the product is private information of the agent, the principal offers the most efficient firm a rent to provide an incentive to manufacture a product of a higher quality. No such rent is given to the less efficient firm. If the health insurer wants a medicinal product of a certain quality, he needs to pay a higher price by giving up a rent to the efficient pharmaceutical manufacturer. The efficient firm's price is set higher by the health insurer than that of the inefficient firm.

Special case: Shut-down of the least efficient type The principal might choose to cease production if the agent is a $\bar{\theta}$ type. The screening of types takes the special form of excluding the least efficient type. The incentives and participation constraints reduce both to $p^s - \underline{\theta q}^s \geq 0$ for the efficient type and $0 \geq p^s - \bar{\theta}q^s$. In this specific case, the inefficient type does not supply which implies that no rent has to be given to the efficient type.

Laffont and Martimort explain that an optimal shut-down policy exists when,

$v(S(\underline{q}^*) - \underline{\theta q}^*) \geq v(S(\underline{q}^{SB}) - \underline{\theta q}^{SB} - \Delta\theta\bar{q}^{SB}) + (1-v)(S(\bar{q}^{SB}) - \bar{\theta}\bar{q}^{SB})$ which implies as $\underline{q}^* = \underline{q}^{SB}$,

$v\Delta\theta\bar{q}^{SB} \geq (1-v)(S(\bar{q}^{SB}) - \bar{\theta}\bar{q}^{SB})$.

Shut-down of the least efficient type is suitable when the expected costs, due to the efficient type's rent, which is caused by its informational advantage are higher than the expected advantage which arises

from transacting with the least efficient type.

Results

Laffont and Martimort's screening model shows how a risk-sharing scheme can be instrumental in making pharmaceutical firms supply a product of a higher quality than they would have under a standard contract when the costs of manufacturing are unknown by the health insurer. In particular, an efficient firm would deliver a product of a higher quality in return for a positive information rent. Whereas with a less efficient firm, responsible for manufacturing a product whose quality is lower than the first-best, the pharmaceutical firm does not get any rent. Laffont and Martimort's screening model applied to pharmaceutical markets shows that, when an efficient pharmaceutical company has private information over the costs of its product, the health insurer has to pay an additional rent for a certain quality of the product to be reached. In this framework, the health insurer is trying to get knowledge on certain private information of the pharmaceutical company.

Recent developments in princing and reimbursement decisions show that health insurers increasingly make use of cost-effectiveness ratios to decide on the price and reimbursement status of new innovative pharmaceuticals. Therefore, it is up to pharmaceutical companies to demonstrate that the cost-effectiveness of their product is higher than a given threshold pre-defined by healthcare authorities. In Germany, the same situation exists for new medicinal products which, since 1 January 2011, have to undergo an early benefit assessment.. In June 2012, the Joint Federal Committee decided on the status of seventeen medicinal products with regard to an early benefit assessment. In September 2012, only one pharmaceutical company came to an agreement with the Mandatory Health Insurance in respect of the pricing of its new medicinal product. By September 2012, four companies had decided to opt out. The consequence of such actions is that no price is set and the medicinal product is not reimbursed (BPI, 2012). Cases where the health insurer and the pharmaceutical company reach different conclusions in their pharmaco-economic assessment of the medicinal product are not rare. During the cost-benefit assessment performed by the health insurer, it is not rare for firms to claim a certain effort on the quality for their product which is not recognised by the health insurer. In some cases, the health insurer might also refuse to reimburse the product due to their lack of confidence in the efforts in terms of R&D allegedly undertaken by the pharmaceutical company. Such cases can happen, for example, when more cost-effective alternatives already exist in the market. The insufficient additional medical benefit found by the health insurer in their pharmaco-economic assessment leads to a refusal to reimburse the product. In 2011, among the products which were assessed by the Transparency Commission in France, only two were considered as innovative, corresponding to an ASMR rating I or II. Indeed, the Health Care Pricing

Committee's 2011 report notes that the number of products assessed as innovative by the Transparency Commission in France have decreased over the year (Annual report CEPS, 2011). Therefore, pharmaceutical firms might consider signaling the effectiveness of their product to the health insurer. In this perspective, the pharmaceutical company initiates the risk-sharing scheme.

A signaling model means that the pharmaceutical company would address the health insurer directly in order to demonstrate the effectiveness of its product. Consequently, this means that - after having been denied reimbursement - the pharmaceutical company offers the health insurer a risk-sharing scheme as a sign that it invested in the quality of the product which is effective. Such an arrangement has already been reached in the Velcade risk-sharing scheme in the UK. While four products - all used in the treatment of MS - have been refused reimbursement, they all offered NICE a signal by proposing a risk-sharing scheme. As mentioned by Barros (2011, p. 462), risk-sharing schemes are used by "firms holding a sufficiently high degree of confidence in their product".

No theoretical economic paper has so far analysed risk-sharing schemes by focusing on the signaling effect played by the implementation of a risk-sharing scheme. The aim of the following model is to show in a signaling model that, by proposing a risk-sharing scheme, pharmaceutical firms are at the same time signaling to health care authorities the investment made to ensure a product of good quality. It can be shown that only a separating equilibrium is possible in contrast to a pooling equilibrium. This conclusion is therefore in favour of implementing risk-sharing schemes to solve the existing hidden information issues.

4.3.2 Structure of the signaling game and assumptions

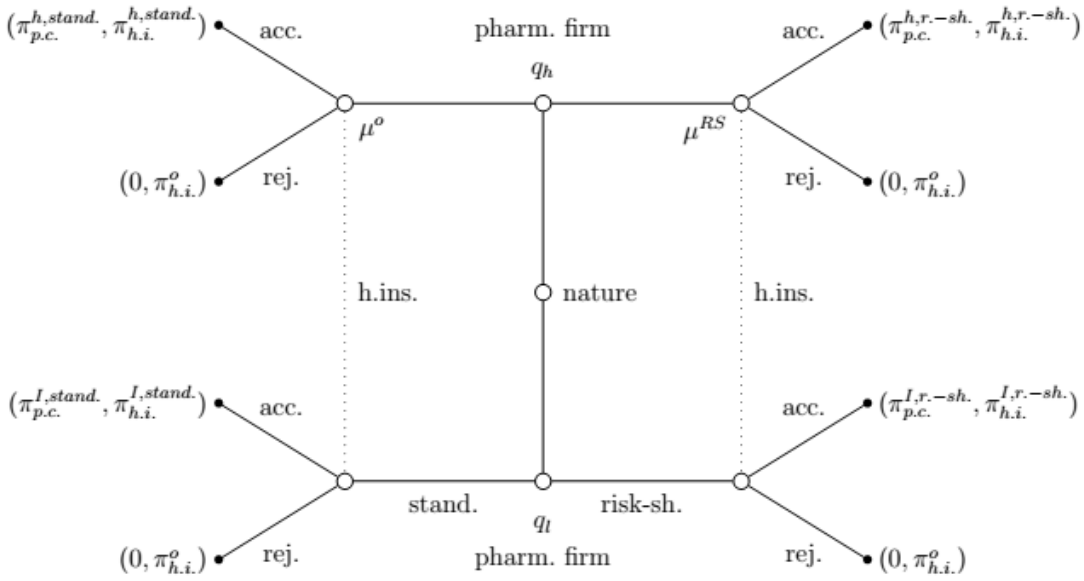
Once the structure of the following signaling model and the assumptions have been described (4.3.2.1), then in a second step, the price-setting stage of the game will be analysed (4.3.2.2) and the different equilibria investigated (4.3.2.3), and finally, the stability of the different equilibria are discussed and conclusions are drawn (4.3.2.4).

4.3.2.1 Assumptions

The following model is considered to be a signaling game where the pharmaceutical company is the sender and the health insurer is the receiver responsible for setting the price and the reimbursement status of a new medicinal product. Figure 4.5 represents the model in a decision model.

If the firm manufactures a new medicinal product at unit cost c and the probability of the product to heal the patient is q, and for simplicity's sake it is assumed that the medicinal product's probability of success can only take two values, q_l and q_h, with $q_l < q_h$, then the sender can be of two types, which are characterised by the respective values of q.

Figure 4.5: Representation of the game



Sources: own representation

It is now of interest to consider the information that the pharmaceutical firm provides to the health insurer. This is specifically related to the type of contract the firm is seeking in relation to the supply of an innovative medicinal product. Two types of contract exist: the first is a risk-sharing scheme contract whereby the terms of the contract specify that the health insurer only pays the price p of the supplied medicinal product if it is successful to treat the patient, the second type is a standard contract where the price of the product is paid to the pharmaceutical company regardless of its success. Consequently, the sender has two possible actions (so-called "messages"). The pay-off in cases where a risk-sharing scheme contract is negotiated, is equal to $qp^{RS} - c$ whereas in a standard contract it corresponds to $p^0 - c$.

The health insurer does not know the q but has an a priori distribution of $(\Pi, 1 - \Pi)$, whereby Π is the probability that the medicinal product's success rate takes the highest value, $q = q_h$. Depending on the type of contract negotiated, the health insurer sets a price p^{RS} or p^0. Where a risk-sharing scheme exists, the corresponding pay-off is equal to $w - d + q(d - p^{RS})$, whereby w represents the utility of the patient for not being sick and d the disutility caused by the disease. In a standard contract, the health insurer's pay-off corresponds to $w - d - p^0 + qd$.

4.3.2.2 Price-setting stage

In order to find the equilibria of the signaling game, the analysis of the price-setting stage must first be performed.

The first possible case is that the health insurer received the signal corresponding to a risk-sharing scheme. If μ^{RS} denotes the health insurer's belief that the product has a high success rate, q_h, then the health insurer's expected pay-off is equal to:

$\mu^{RS}(w - d + q_h(d - p^{RS})) + (1 - \mu^{RS})(w - d + q_l(d - p^{RS}))$.

$\iff w - d + (\mu^{RS} q_h + (1 - \mu^{RS})q_l)(d - p^{RS})$.

This expression is valid when it is profitable for the health insurer to set the price at a level acceptable to the pharmaceutical company, regardless of the probability of success q_h or q_l. For type l, the price will be accepted when it is not set lower than $\frac{c}{q_l}$. The price derived from the health insurer's pay-off function will be set equal to $p_b^{RS} = \frac{c}{q_l}$. At this price, both types accept the risk-sharing scheme. However, if the health insurer finds it profitable to set a price lower than $\frac{c}{q_l}$, the firm will accept only if $q = q_h$. In this case, the corresponding pay-off is $w - d + \mu^{RS}(d - p^{RS})$ with a price $p_1 = \frac{c}{q_h}$. By comparing both expressions, it is profitable for the health insurer to set the price $p^{RS} = p_1^{RS}$ when,

$(\mu^{RS} q_h + (1 - \mu^{RS})q_l)(d - p_b^{RS}) < \mu^{RS} q_h (d - p_1^{RS}) \iff \frac{q_l d - c}{q_l d - c + c(\frac{q_h}{q_l} - 1)} < \mu^{RS}$.

Assuming that $c < q_l d$, the left hand side of this inequality is denoted by $\bar{\mu}^{RS}$, then:

$p^{RS} = p_b^{RS} = \frac{c}{q_l}$for $\mu^{RS} \leq \bar{\mu}^{RS}$ and

$p^{RS} = p_1^{RS} = \frac{c}{q_h}$ for $\mu^{RS} > \bar{\mu}^{RS}$.

If the health insurer is approached by the pharmaceutical company with a standard contract, where μ^0, is the health insurer's belief that $q = q_l$, then the pay-off is equal to

$\mu^0(w - d - p^0 + q_h d) + (1 - \mu^0)(w - d - p^0 + q_l d) = w - d - p^0 + (\mu^0 q_h + (1 - \mu^0)q_l)d$

In a standard contract, the price set by the health insurer does not depend on the health insurer's belief μ^0, and is equal to $p^0 = c$. Hence both types accept the price.

4.3.2.3 Analysis of the existing equilibria

It will now be investigated, whether a separating or a pooling equilibrium exists; only pure-strategy equilibria will be studied.

- First case (RS, 0): Risk-sharing scheme if $q = q_h$ and standard contract if $q = q_l$

Starting with separating equilibria, the most relevant case will be studied firstly, where the firm offers a risk-sharing scheme contract if $q = q_h$ and a standard one if $q = q_l$. In this case, perfect Bayesian

equilibrium requires $\mu^{RS} = 1$ and $\mu^0 = 0$. As $1 > \bar{\mu}^{RS}$, prices are respectively $p^{RS} = \frac{c}{q_h}$ and $p^0 = c$. Hence, the pay-off for type h is equal to:

$q_h p^{RS} - c = c - c = 0$

If the high-quality type asks for a standard contract, the corresponding pay-off will be $p^0 - c = c - c = 0$

If the low-quality type offers a risk-sharing scheme, the respective pay-off will be equal to:

$q_l p^{RS} - c = \frac{q_l}{q_h} c - c < 0$

and the corresponding pay-off of l by offering a standard contract:

$p^0 - c = c - c = 0$.

Hence, the case (RS,0) represents a separating equilibrium.

- Second case (0, RS): Risk-sharing scheme if $q = q_l$ and standard contract if $q = q_h$

An example where the type h offers a standard contract and type l offers a risk-sharing scheme will now be reviewed. The respective beliefs of the health insurer are $\mu^{RS} = 0$ and $\mu^0 = 1$ which implies the following prices $p^{RS} = \frac{c}{q_l}$ and $p^0 = c$.

The respective pay-off of h for offering a risk-sharing scheme and a standard contract are equal to

$q_h p^{RS} - c = \frac{q_h}{q_l} c - c > 0$ for a risk-sharing scheme, and

$p^0 - c = c - c = 0$, for a standard contract.

As the type h prefers a risk-sharing scheme, the case (0, RS) cannot be an equilibrium.

- Third case (0, 0): Both types offer a standard contract

Pooling equilibria will now be analysed. First an example where both types offer a standard contract (0,0) is analysed. In this example, beliefs are equal to $\mu^0 = \Pi$ and μ^{RS} is arbitrary. Therefore, two cases will be distinguished, whether $\mu^{RS} \leq \bar{\mu}^{RS}$or $\mu^{RS} > \bar{\mu}^{RS}$. For $\mu^{RS} \leq \bar{\mu}^{RS}$, corresponding prices are $p^{RS} = \frac{c}{q_l}$ and $p^0 = c$. Consequently, profits for type h whether a risk-sharing scheme contract or a standard contract is offered are respectively equal to $q_h p^{RS} - c = \frac{q_h}{q_l} c - c > 0$ and $p^0 - c = c - c = 0$. It follows that (0, 0) is not an equilibrium for $\mu^{RS} \leq \bar{\mu}^{RS}$.

If $\mu^{RS} > \bar{\mu}^{RS}$, then the corresponding prices are equal to $p^{RS} = \frac{c}{q_h}$ and $p^0 = c$. Profits of type h offering a risk-sharing contract are equal to $q_h p^{RS} - c = c - c = 0$ which is similar to type h offering a standard contract $p^0 - c = c - c = 0$. For type l, profits through offering a risk-sharing scheme are equal to $q_l p^{RS} - c = \frac{q_l}{q_h} c - c < 0$ and by offering a standard contract equal to $p^0 - c = c - c = 0$. Thus, (0,0) corresponds to a pooling equilibrium with $\mu^{RS} > \bar{\mu}^{RS}$.

- Fourth case (RS, RS): Both types offer a risk-sharing scheme

Finally, the last possible case will be investigated, where both types offer a risk-sharing scheme (RS, RS). For this configuration to constitute an equilibrium, the respective beliefs of the health insurer are as follows: $\mu^{RS} = \Pi$ and μ^0 is arbitrary. As in the previous case, two situations have to be considered, whether $\Pi \leq \bar{\mu}^{RS}$or $\Pi > \bar{\mu}^{RS}$. For $\Pi \leq \bar{\mu}^{RS}$, corresponding prices are $p^{RS} = \frac{c}{q_l}$ and $p^0 = c$. Thus, profits for type h for respectively offering a risk-sharing scheme and a standard contract are equal to $q_h p^{RS} - c = \frac{q_h}{q_l}c - c > 0$ and $p^0 - c = c - c = 0$. For the type l, the profits with a risk-sharing scheme are equal to $q_l p^{RS} - c = c - c = 0$ and with a standard contract $p^0 - c = c - c = 0$. Therefore (RS, RS) also represents a pooling equilibrium if $\Pi \leq \bar{\mu}^{RS}$.

For $\Pi > \bar{\mu}^{RS}$, respective prices are $p^{RS} = \frac{c}{q_h}$ and $p^0 = c$. Consequently, profits of the type h are equal to $q_h p^{RS} - c = c - c = 0$ with a risk-sharing scheme and $p^0 - c = c - c = 0$ with a standard contract. Profits of the low-quality type l are equal to $q_l p^{RS} - c = \frac{q_l}{q_h}c - c < 0$ with a risk-sharing scheme and $p^0 - c = c - c = 0$ with a standard contract. Hence, (RS, RS) is not an equilibrium if $\Pi > \bar{\mu}^{RS}$.

Intermediate conclusion Summarising the results, the cases (RS, 0), (0,0) with $\mu^{RS} > \bar{\mu}^{RS}$ and (RS, RS) with $\Pi \leq \bar{\mu}^{RS}$ are all perfect Bayesian equilibria. This implies that risk-sharing contracts can be interpreted as the pharmaceutical firm's signaling a product of high quality, as (RS, 0) is an equilibrium in the game. However, the pooling equilibrium (RS, RS) also exists for $\Pi \leq \bar{\mu}^{RS}$and (0, 0). In this case, the observation of offering a risk-sharing scheme does not signal anything.

4.3.2.4 Analysis of the stability of the equilibria and conclusions of the signaling game

In respect of the separating equilibrium (RS, 0), it is interesting to note that from an ex-ante point of view, the configuration (RS,RS) with $\Pi \leq \bar{\mu}^{RS}$) leads to a lower expected pay-off to the insurer than (RS, RS). This can be shown by noting that, in the case (RS, 0), the health insurer's pay-off is equal to $w - d + q_h(d - \frac{c}{q_h})$ if $q = q_h$ and $w - d + q_l d - c$ if $q = q_l$ (standard contract). Hence, using a priori beliefs, the expected pay-off is equal to

(*) $w - d - c + (\Pi q_h + (1 - \Pi)q_l)d$.

In the case of (RS, RS), with $\Pi \leq \bar{\mu}^{RS}$, pay-offs are equal to $w - d + q_h(d - \frac{c}{q_l})$ if $q = q_h$ and $w - d + q_l(d - \frac{c}{q_l})$ if $q = q_l$, leading to the expected pay-off $w - d + (\Pi q_h + (1 - \Pi)q_l)d - c((1 - \Pi) + \Pi\frac{q_h}{q_l})$.This expression is obviously smaller than the expression (*).

This means that the health insurer has an incentive to attain (RS, 0) rather than (RS, RS). In order to reach this, the health insurer can publicly express a very optimistic (a priori) belief, $\Pi > \bar{\mu}^{RS}$. By publicly expressing its optimistic beliefs, the health insurer makes the type l afraid of offering a risk-sharing scheme. This also implies that the health insurer has the means to steer from the less advantageous situation (RS,

RS) to the more profitable (RS, 0). Consequently, the equilibrium (RS, 0) is more likely than (RS, RS).

Finally, with regard to the (0, 0) equilibrium, there is no reason to dismiss it within the restrictive framework set in this model. Expected pay-offs are the same for cases (RS, 0) and (0, 0) as can be easily verified. However, the price-setting in both cases differs in complexity. Consequently, the standard contract's objective is basically to cover costs without having to assess q. In real circumstances, q cannot be assessed in a satisfactory manner. Due to this fact, which might be an issue in particular for highly innovative medicinal products, insurers might as a consequence choose security margins on top of the prices in the above model - as a risk-sharing scheme is strictly preferred by type h. In this configuration, (0, 0) does not represent an equilibrium anymore. Hence, (0,0) does not appear to be a stable equilibrium. However, an exact analysis that would have to explicitly take the uncertainty about q_h and q_l into account is obviously beyond the scope of the above model and also beyond the scope of the work.

4.3.3 Policy implications

Three different models with different underlying assumptions have been developed to show to which extent risk-sharing schemes can be a useful instrument in solving information asymmetries. While these three models correspond to different situations (4.3.3.1), the results found are put into perspective with the actual use and success of risk-sharing schemes and some trends concerning the growth of such schemes are presented (4.3.3.2).

4.3.3.1 Risk-sharing schemes as an instrument to solve information asymmetries

In the previous two sections, it was shown that risk-sharing schemes can be used by health care authorities to solve the information asymmetries existing in pharmaceutical markets, in particular hidden action concerning the incentives to innovate and hidden information on the product's effectiveness. This impact of risk-sharing schemes is important and will be taken into account by health care authorities. Indeed for new innovative products - which are often expensive - the health care authorities are uncertain on the effectiveness of the product and on the pharmaceutical firms' underlying incentives to continually invest in their new product. In this specific case, risk-sharing schemes are particularly effective and will be considered as a real alternative to standard price setting.

The principal-agent model and the signaling model can be regrouped as the signaling model might be considered as corresponding to the first stage of the principal-agent model described in the section 4.2. Pharmaceutical companies have private information over their products. Therefore, before the health insurer decides to propose a standard contract or a risk-sharing scheme, the pharmaceutical company can send a signal concerning the efficacy of its product.

The three models presented have in common that they confirm Antonanzas (2011, 2013) results. When the pharmaceutical company has private information over its product, the health insurer has to pay the price and give a rent to efficient pharmaceutical manufacturers to provide them with incentives to offer a product of a higher quality.

Limitations However, an important restriction will be stressed as these results only hold when the information is asymmetrically distributed and not in the symmetric case. If the information is symmetric, meaning that neither the pharmaceutical company nor the health insurer knows about the pharmaceutical product's effectiveness, no conclusion can be drawn. The failure of the Multiple Sclerosis risk-sharing scheme for beta-interferons and glatiramer acetate might be explained by this, meaning that, due to the characteristics of pharmaceutical products as "experience goods", nor does the pharmaceutical company know with any certitude the effectiveness of its new product. In the case of the Multiple Sclerosis risk-sharing scheme, which consisted of four drugs that allegedly reduced by one third the number of relapses so that the patients required less hospital treatment. Following NICE's assessment that the product was not cost-effective, a risk-sharing scheme was implemented in 2001 and an interim report was issued based on two years of data. The report concluded that there was little evidence that the scheme's medicinal products effectively delayed the disease's progression. The report also mentioned that these drugs might even have worsened some patients' conditions (NICE). However, these results were also very dependent on the methodology and the robustness of the data, which were considered deficient. For this reason, no price cut was decided.

4.3.3.2 Growing trend towards risk-sharing schemes for innovative medicinal products

Theoretical literature and empirical studies on the impact of the implementation of risk-sharing schemes on innovation in the pharmaceutical industry are scarce. The reason for this is that - as mentioned by Espin et al. (2011) - as a result of risk-sharing schemes for oncology products in particular, such agreements offer a new instrument for financing costly innovative medicinal products. Therefore, most of the schemes implemented are financially-based and not performance-based schemes. However, a trend exists towards newer performance-based risk-sharing schemes. Consequently, the impact on innovation is more indirect as firms which are engaged in a performance-based risk-sharing scheme have incentives to create innovative products in order to achieve high prices. Espin et al. mention that only three countries in the EU performed empirical studies on the impact of risk-sharing schemes, France, Italy, and Portugal. As financial-based risk sharing schemes are mostly implemented in France and in Portugal, the results of the respective studies are of no interest with regard to promoting innovation. Whereas in Italy, the study

performed by the Italian health care authorities focused on the economic (time to market for availability) and geographical aspects (regional disparities in the availability of the products) and the impacts of the agreements on innovation aspects were not mentioned.

CONCLUSION OF CHAPTER 4

Risk-sharing schemes are a widespread instrument and can be considered - due to their impact on moral hazard and adverse selection issues - as a useful measure in the sharing of the financial uncertainty in respect of the effectiveness of innovative products. While such schemes are more administratively burdensome than the usual price-setting, they can be used as an efficient way to alleviate moral hazard issues linked to the pharmaceutical companies' incentives to innovate and adverse selection issues in the effectiveness of innovative medicinal products in pharmaceutical markets. This result only holds true where the information is asymmetrically distributed, meaning that the pharmaceutical company - as the manufacturer of the product - has private information on its product and is dependant on the levels of the other costs incurred. While such schemes usually contain confidentiality clauses, it seems that the practice and the trends confirm the results found. Such a widespread use of risk-sharing schemes among member states for innovative medicinal products should be parallel with an evolution in the development of HTA assessments, and in particular an exchange of good practices and more transparency in the assessments in order to provide pharmaceutical firms more visibility in their R&D decisions.

Chapter 5

CONCLUDING REMARKS

Interdependance between off- patent and on-patent markets

The empirical study performed in the second chapter had two main objectives. The first was to review the criteria used by the EC to define the scope of the relevant market and, in particular which criteria justify departing from ATC level 3 (therapeutic substitution). The second objective was to investigate whether the EC tended to define narrower markets, and if so, which were the important demand-side criteria to define a very narrow market at the molecule level (ATC level 5). Consequently, those demand-substitution criteria which were found are also useful in analysing policy measures based on demand-substitution patterns. Cost-containment measures, such as internal reference-pricing or regulations concerning generics, often require clustering products together, dependent upon their substitutability for the patient.

The analysis of demand-substitution patterns within pharmaceutical markets also highlighted the existing segmentation between off-patent and on-patent markets, which was further investigated in chapters three and four, with the study of two measures, the reference pricing system and risk-sharing schemes. By analysing the impact of both measures on pharmaceutical companies´ innovation's incentives, and on the information asymmetries arising in pharmaceutical markets, whether in the form of an information advantage, or hidden information around the effectiveness of the product, it was shown that these measures targeting off-patent and on-patent markets were complementary.

Therefore, by increasing the price elasticity of demand, the implementation of a reference pricing scheme partially counterbalances the off-patent originator´s information advantage and gives incentives to pharmaceutical firms to enter into price competition, rather than focusing on marketing expenses. However, complementary measures are also necessary in innovative markets to fully repeal the effect of an information advantage. In particular, the analysis performed in chapter three indicated in which cases a

reference price scheme can promote major innovations. By creating a specific pricing and reimbursement framework for innovative and non-innovative medicinal products, and in particular, by excluding innovative medicinal products from being included in the reference price, reference pricing schemes represent a setback scenario for innovative medicinal products. While reference pricing is an efficient policy to contain costs and increase price competition, it needs to be backed up with other policies promoting innovative medicinal products in on-patent markets.

The fourth chapter analysed the impact of a risk-sharing scheme on adverse selection and moral hazard issues, by focusing on the uncertainty around the effectiveness of innovative products. The analysis showed that the implementation of a risk-sharing scheme provides pharmaceutical companies with innovation incentives and represents a solution to share the pharmaceutical company´s private information on the effectiveness of its medicinal product.

A segmentation between off-patent and on-patent medicinal products is increasingly growing through the various measures being implemented. In off-patent medicinal markets, the aim is, through a rational use of medicines, to decrease healthcare expenditure by cutting prices and promoting generics. In on-patent markets, the purpose of the different measures is to contain costs by better assessing the added medical value of innovative products and promoting major innovations, in order to obtain value for money and enable patients to have timely access to innovative products.

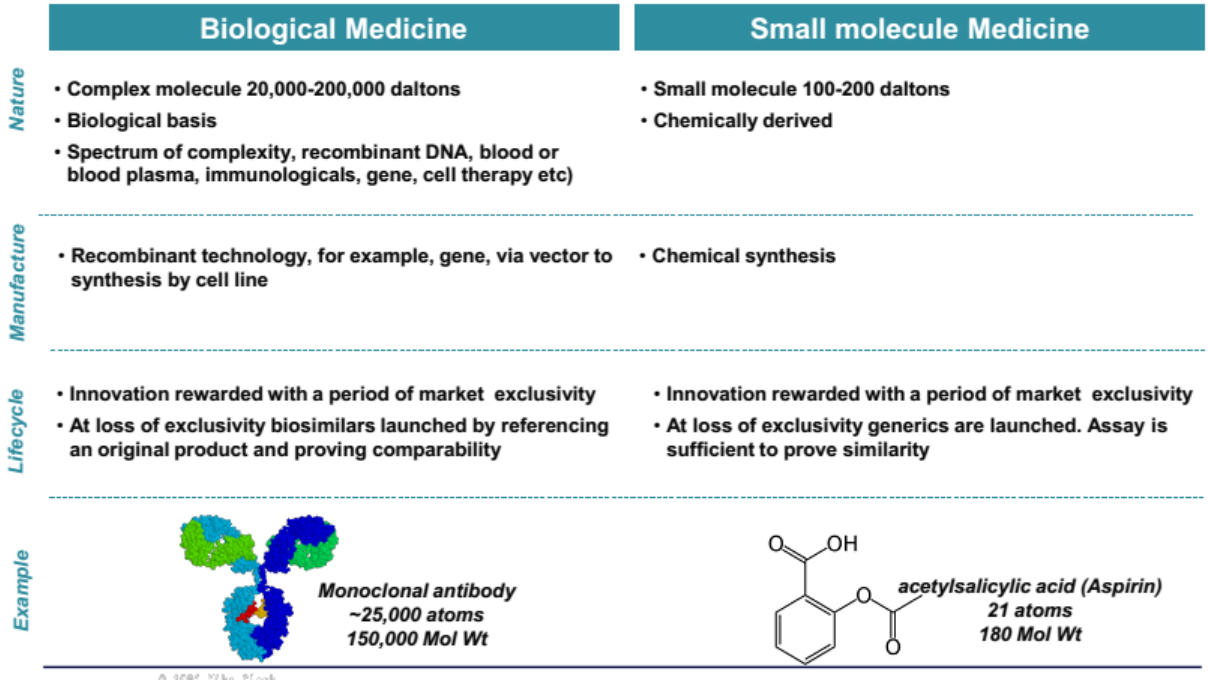
The analysis of the relevant markets performed, and the in-depth study of two widespread measures, show a significant shift from supply-driven reimbursement systems to demand-driven reimbursement systems. The complementarity of the different markets also stressed the importance of involving all stakeholders in the value chain of the medicinal products, including wholesalers, physicians and pharmacists, in order to have a sustainable healthcare system providing service of a high quality, at affordable prices.

Further research: Biologics and biosimilars - Issues around substitutability and interchangeability

This research focused on chemical medicinal products. However, it would also be interesting from competition point of view to investigate competition patterns within biologic markets whose potential, in terms of medical progress for patients as well as sales volumes worldwide, are gaining in importance. Their specific characteristics, which lead to distinct competition patterns from chemical medicinal products, have a different market dynamic than chemical products. They are of particular interest from an economic and competition analysis standpoint due to the market entry of biosimilars.

A biological substance can be described as: “a substance that is produced by or extracted from a

Figure 5.1: Comparison between biologic and chemical medicinal products



Sources: IMS, 2012

biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control." (Directive 2001/83/EC Annex I, 3.2.1.1b)).

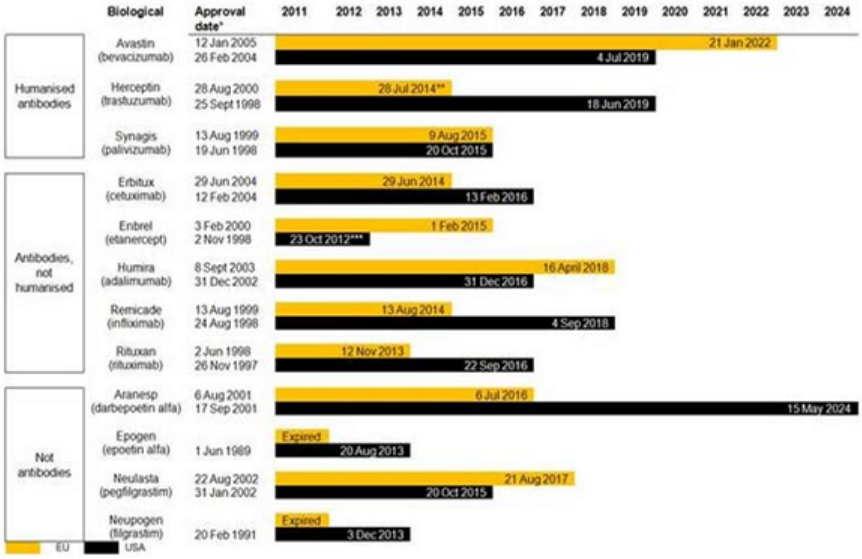
Figures 5.1 summarises the main differences between biological and chemical medicinal products. Biological medicinal products differ from other medicinal products as their active substance comes from a biological substance and not from a chemical one, as it is the case for pharmaceutical products. Therefore, biologicals are products such as blood factors, thrombolytic agents, hormones, haematopoietic growth factors, interferons, interleukin-based products, vaccines, and monoclonal antibodies.

Patents and data protection for several biologics have already expired and several others are due to expire in the coming years so it can be excpected that they will be copied by firms possessing the required technological competencies (cf. figures 5.2).

Copies of biologicals are similar biological medicinal products, so-called biosimilars. The first biosimilars on the market were copies of endogenous human proteins (erythropoietin, insulin, growth hormones and cytokines) developed with recombinant DNA. In the EU, mid-2013, 12 biosimilars have been granted a marketing authorisation by the EMA[1].

[1]Cf. EMA, available at http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&murl=menus%2Fmedicines%2Fmedicines.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&alreadyLoaded=true last accessed september 2013.

Figure 5.2: Expiry dates of patent for twelve major biologicals



Sources: IMS, 2012

Contrary to generics which are copies of conventional medicinal products - and possess a chemical origin and are bioequivalent copies of medicines - biosimilars are made of complex biological molecules which are comparable but not seen as identical to the licensed biologicals. Making an exact copy is impossible as the active ingredient can never be exactly the same as the biological originator. The obtention of a marketing authorisation for biosimilars requires costly investments in clinical developments. Differences linked to the variability of the raw material and to the manufacturing process exist. The method used to demonstrate the bioequivalence and interchangeability is different from that required for conventional generics. Therefore, in the case of biosimilars, it is not only the active substance which is important, but also the manufacturing process which has an impact on the legal and regulatory framework for manufacturers of biosimilars. Consequently, the EMA lays down in specific guidelines the requirements concerning the manufacturing process and the specificity a product has to fulfill in order to be considered as similar to another already marketed product in terms of quality, safety, and efficacy [2]. The 2005 EMA guideline on similar biological medicinal products containing biotechnology-derived proteins as an active substance stresses that, for biosimilars, comparisons at the active substance and finished product level are insufficient. While the biosimilar manufacturer may refer to previous non-clinical and clinical data of the comparative product in the comparability exercise, they will however be required to provide additional non-clinical and clinical data (EMA Guideline, 2005, p.3). Further to the existence of a general guideline,

[2]The legal basis is the Directive 2003/63/EC amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human with provisions on biosimilars into an Annex (Section 4, Part II) and the Directive 2004/27/EC specifying the modalities for a biosimilar to be marketed.

Figure 5.3: Authorised biosimilars in the EU (2013)

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An Agency of the European Union

15/09/2013

Medicine Name	Active Substance	Common nam	Atc code	Marketing Authorisation H	Status	Authorisation dat	Indication
Abseamed	epoetin alfa	epoetin alfa	B03XA01	Medice Arzneimittel Pütter G	Authorised	28/08/2007	Treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adult and paediatric patients
Binocrit	epoetin alfa	epoetin alfa	B03XA01	Sandoz GmbH	Authorised	28/08/2007	Treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adult and paediatric patients
Biograstim	filgrastim	filgrastim	L03AA02	CT Arzneimittel GmbH	Authorised	15/09/2008	Biograstim is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy
Epoetin Alfa Hexal	epoetin alfa	epoetin alfa	B03XA01	Hexal AG	Authorised	28/08/2007	Treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adult and paediatric patients
Filgrastim Hexal	filgrastim	filgrastim	L03AA02	Hexal AG	Authorised	06/02/2009	Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy
Nivestim	filgrastim	filgrastim	L03AA02	Hospira UK Ltd.	Authorised	08/06/2010	Filgrastim is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy
Omnitrope	somatropin	somatropin	H01AC01	Sandoz GmbH	Authorised	12/04/2006	Growth disturbance due to insufficient secretion of growth hormone (GH).
Ratiograstim	filgrastim	filgrastim	L03AA02	Ratiopharm GmbH	Authorised	15/09/2008	Ratiograstim is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy
Retacrit	epoetin zeta	epoetin zeta	B03XA01	Hospira UK Limited	Authorised	18/12/2007	Treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adult and paediatric patients:
Silapo	epoetin zeta	epoetin zeta	B03XA01	Stada Arzneimittel AG	Authorised	18/12/2007	Treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adult and paediatric patients
Tevagrastim	filgrastim	filgrastim	L03AA02	Teva Generics GmbH	Authorised	15/09/2008	Tevagrastim is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy
Zarzio	filgrastim	filgrastim	L03AA02	Sandoz GmbH	Authorised	06/02/2009	Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy

Sources: EMA, 2013

product-specific guidelines also exist[3].

The German Pharmaceutical Association for Generics, ProGenerika[4], estimated the costs of developing a biosimilar from €80 million to €120 million , which represents more than ten times the costs of developing a generic medicinal product[5]. Manufacturing biosimilars leads to higher and more variable costs, as the manufacturing process includes biological elements, such as fermentation or cell culture, and requires extensive clinical trials. Consequently, price reduction compared to their biologic comparator is expected to be lower than in the case of generics.

Competition patterns between biologics and biosimilars are not only important for legal and health concerns but also for economic policy purposes as they may have the potential to provide important costs savings for third party payers, especially through price competition. Consequently, Grabowski, Ridley and Schulman (2007) investigated the extent to which biosimilars may drive the prices of biologics down by analysing the entry of firms into the biologics market. By modeling generic biological competition and estimating market entry by taking into account the existence of important fixed and variable costs as well as the market size, they found that there will be less competition than in generic markets for pharmaceuticals after patent expiration, leading to a light price decrease in the market for biologicals. From the number of entrants in the market, they estimated the price of the generic product to be 44% of the price of the originator product and the price of the biosimilar to be 82% of the price of the comparative biologic. Not only are biologic manufacturers less likely to enter the market but the price decrease of biosimilars compared to generics is less important, leading to a lower competitive environment. Grabowski et al. stress, however, that their model has to be seen as an illustration of the impact of fixed costs for market entry and not as a forecast of the evolution of the biologicals market and their prices. By fixed costs, they referred to three special costs which are: clinical costs, capital costs, and manufacturing costs. With regards to generics, only the latter is relevant, but these costs are quite low. Their results are in line with current price developments, as shown in figure 5.4.

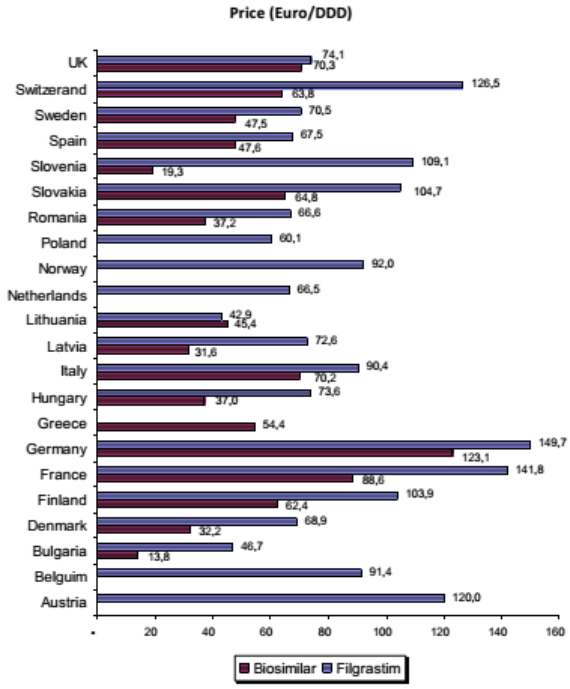
These specifics of biosimilars, when compared to chemical medicinal products, has an impact on the definition of the relevant market. In the merger case COMP/M.5865 Teva/Ratiopharm (recital 28 and 29), the EC mentions that the manufacturing and marketing of a biosimilar product is more complex and time-consuming (from six to eight years) than for a generic product. It also requires important upfront investments which represent a barrier to entry for biopharmaceutical firms. Furthermore, the regulatory approval and marketing procedure of a biosimilar resemble more closely that of an originator product.

[3]Product-specific guidelines concern for example monoclonal antibodies, recombinant erythropoietins, cf. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002958c&jsenabled=true.

[4]Cf. http://www.progenerika.de/.

[5]Cf. newsletter "profil", 01/2011, April, http://www.progenerika.de/downloads/9377/ProGenerikaNewlProfil.pdf.

Figure 5.4: Prices of Filgastrim and biosimilar in the EU (in €, 2009)



Sources: EMINET, 2011

Figure 5.5: Biosimilar market in the EU (in thousand €, 2011)

Year	Originators (ref. products)	Biosimilars	Total	% Biosimilars
2007	973.538	3.294	976.832	0.34
2008	949.091	18.023	967.114	1.86
2009	921.198	65.506	986.705	6.64

Sources: EMINET, 2011

Hence, a biosimilar is required to perform clinical trials to receive marketing approval, while this is not the case for a generic of a chemical originator product. Biosimilars differ from generics so that their inclusion in the same relevant market as their originator, as this is the case for originators and generics, is not as straightforward for biologics. Biologic markets are still new and their developments, as well as the evolution of the manufacturing process may change this analysis. For the time being, the market for biosimilars is not mature, but it has a very large potential, even with the existing large barriers to entry, as shown in figure 5.5, and should therefore be carefully monitored.

The first generation of biologics is already confronted with the new generation of biologic products, so-called biobetters, which biosimilars firms are also trying to develop. The development of the biosimilar market in the US is still more constrained than in the EU, given the lack of, or weak pre-existing legal pathway. The EU is, for the time being at least, a step ahead of the US. The "Biologics Price Competition and Innovation Act", of 23 March 2010 within the "Patient Protection and Affordable Care Act" does

not represent any practical pathway given by the FDA yet[6]. This new legislation[7] creates an abbreviated legal pathway for biologicals that are considered as "biosimilar" to or "interchangeable" with biological products licensed by the FDA (Muller, Shea, 2010). Under the BPCI Act, a biologic can be demonstrated to be "biosimilar" to an originator product if the data shows that the product is "highly similar" to the originator biologic product. If this is not the case, the biological product is considered as "interchangeable" with the reference product. The FDA will play a central role regarding the criteria to prove whether the biological is highly biosimilar or even interchangeable. This distinction is essential, as only interchangeable biologics may be substituted.

[6] Cf. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215089.htm.

[7] Cf. the section "Biologics Price Competition and Innovation Act" (BPCI Act) at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ Biosimilars/default.htm.

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ANNEXES

DESCRIPTION OF THE VARIABLES USED

	Explanatory variables
ATC3S	*ATC starting level 3* = Classification provided by the parties in the file. Corresponds to the starting-point for the definition of the relevant market.
	Reasons behind EC's decisions (substitution criteria- multiple reasons possible)
IUDG	*Intended use and disease gravity* : Intended use of the products (first-line/second-line treatments) and gravity of the disease are relevant criteria. 1: Yes or 0: No
EFF	*Efficacy:* Efficacy (corresponding to new generation molecules, new modes of actions, and price differences) is a relevant criterion.
AI	*Active ingredient:* Active ingredienght/molecule is a relevant criterion.
OTC	*Existence of Over-the-counter products* : Presence of OTC which can exert a competitive pressure is a relevant criterion.
galform	*Galenic form:* Galenic form is a relevant criterion
ChannelM	*Channel mode* : Channel mode (hospital or pharmacy marekt) is a relevant criterion
EcoReg	*Economic regulation:* Economic regulation, often country specific, is a relevant criterion.
SupplyS	*Supply-substitution patterns:* Supply substitution patterns are a relevant criterion.
	Control variables
Date	*Year*: Year of the merger decision
Art	*Article:* It can either be 6(1)(b) - in case the concentration does not raise serious doubts and as to its compatibility with the common market-, or art. 6(2) it raises serious doubts and proceedings begin.
OTCEXCL	*Exclusively OTC*: ATC category contains only OTC
TO	*Turn-over*: Community-wide turn-over, in million Euro (a).
PrevDec	*Previous decisions* : EC takes as a basis for the market definition the conclusions of one similar precedent case.
VP	*Views of the parties. Value* 1: agree, 0: disagree, with the starting point of the EC.
VPdec	*Confirmation of the views of the parties*: value 1: yes, 0: no
merg reg	*Merger regulation:* Cases investigated under ECMR (2004) take the value 1, and those under and regulation of 1989 with 0.
ATC3MA	*Number of products at the ATC level 3* with a centralised marketing autorisation
ATC4	*Number of ATC 4 classes* existing in the ATC 3 starting point
ATCdes	*Description of ATC level 3* : ATC starting level for the EC's analysis. Value 1= ATC level correspond to AZC 3, Value 0= ATC starting level already departs from ATC 3 and is already narrower.(case of molecule-only markets, only OTC, on galenic indications…)
	Explained Variable
ATCC	*ATC level choice*: ATC level chosen or indicated by the EC (in case of strong indications, but market definition left open)- Value: 1 = ATC level 4 or narrower, or value 0 = ATC level 3 oder broader. In the sub-sample 2004-2011: value 2 = ATC level 5

NOTES:
(a) Before 1999, turn-over was expressed in ECU and no precise figure was available.

	EXPLAINING VARIABLES																				VARIABLE EXPLAINED
													Demand-side substitution								
Mergers	ATC 3S	ATC3_MA	ATC4	ATCdes	OTCEXCL	Art.	Year	MergReg	TO	PrevDec	PrevDecCon	VP	VPDec	IUDG	EFF	AI	OTC	Galform	Channelm	EcoReg	SupplyS	ATCCnarr
M.555	A4A	3	2	0	0	6.1.b	1995	0	.	.	.	.	.	1	0	0	0	0	0	0	0	0
	N2C	0	2	0	0	6.1.b	1995	0	.	.	.	0	0	1	0	0	0	0	0	0	0	0
M.1403	C7A	1	0	1	0	6.1.b	1999	0	.	1	0	0	0	1	0	0	0	0	0	1	1	0
	C7B	0	3	1	0	6.1.b	1999	0	.	1	0	0	0	1	0	0	0	0	0	1	1	0
	C8A	3	0	0	0	6.1.b	1999	0	.	.	.	0	0	1	0	0	0	0	0	0	0	0
	C8B	0	4	0	0	6.1.b	1999	0	.	.	.	0	0	1	0	0	0	0	0	0	0	0
	N1A	9	2	0	0	6.1.b	1999	0	.	.	.	1	1	1	0	0	0	0	0	0	0	0
	N1B	1	4	0	0	6.1.b	1999	0	.	.	.	1	1	1	0	0	0	0	0	0	0	0
M.1397	G4B	13	0	0	0	6.1.b	1999	0	5661	.	.	1	1	1	0	0	0	0	0	0	0	0
M.1835	A5B	0	0	0	0	6.1.b	2000	0	15338			1	1	1	0	0	0	0	0	0	0	0
	B1C	0	6	0	0	6.1.b	2000	0	15338	1	1	0	1	1	0	0	0	0	0	0	0	1
	C3A	0	6	0	0	6.1.b	2000	0	15338	1	1	1	1	1	0	0	0	0	0	0	0	0
	D10 A	2	0	0	0	6.1.b	2000	0	15338	.	.	1	1	1	0	0	0	0	0	0	0	0
	G1A	0	3	0	0	6.1.b	2000	0	15338	.	.	1	1	1	0	0	0	0	0	0	0	0
	G3D	0	0	0	0	6.1.b	2000	0	15338	.	.	1	1	1	0	0	0	0	0	0	0	0
	H2A	0	3	0	0	6.1.b	2000	0	15338	.	.	1	1	1	0	0	0	0	0	0	0	0
	M1A	12	3	0	0	6.1.b	2000	0	15338	.	.	1	1	1	0	0	0	0	0	0	0	0
	N2A	4	0	0	0	6.1.b	2000	0	15338	.	.	0	1	0	1	0	0	1	1	0	0	1
M.1846	J5B	0	6	0	0	6.1.b	2000	0	24651	.	.	0	0	1	0	0	0	0	0	0	0	0
	D6D	0	2	0	0	6.1.b	2000	0	24651	.	.	1	1	1	0	0	0	0	0	0	0	0
	A4A	3	2	0	0	6.1.b	2000	0	24651	.	.	0	0	1	0	0	0	0	0	0	0	0
	P1D	0	2	0	0	6.1.b	2000	0	24651	.	.	1	1	1	0	0	0	0	0	0	0	0
	R1A	2	8	0	0	6.1.b	2000	0	24651	.	.	0	1	1	0	0	0	0	0	0	0	1
	A2B	17	5	0	0	6.1.b	2000	0	24651	.	.	.	.	1	0	0	0	0	0	0	0	0
	N3A	13	0	0	0	6.1.b	2000	0	24651	.	.	1	1	1	0	0	0	0	0	0	0	0
	D6A	1	0	0	0	6.1.b	2000	0	24651	.	.	0	0	1	0	0	0	0	0	0	0	0
	N4A	0	0	0	0	6.1.b	2000	0	24651	.	.	1	1	1	0	0	0	0	0	0	0	0
	R5C	0	0	0	0	6.1.b	2000	0	24651	.	.	.	.	1	0	0	0	0	0	0	0	0
M.1878	A2A	0	7	0	0	6.1.b	2000	0	27329	.	.	1	1	1	0	0	0	0	0	0	0	0
	A7A	0	0	0	0	6.1.b	2000	0	27329	.	.	1	1	1	0	0	0	0	0	0	0	0
	C8A	0	0	0	0	6.1.b	2000	0	27329	1	1	0	0	1	0	0	0	0	0	0	0	0
	C10A	14	4	0	0	6.1.b	2000	0	27329	.	.	1	1	1	0	0	0	0	0	0	0	0
	J1F	1	0	0	0	6.1.b	2000	0	27329	.	.	1	1	1	0	0	0	0	0	0	0	0
	N7D	0	2	0	0	6.1.b	2000	0	27329	.	.	1	1	1	0	0	0	0	0	0	0	0
	P1B	0	0	0	0	6.1.b	2000	0	27329	.	.	1	1	1	0	0	0	0	0	0	0	0
	P1E	0	0	0	0	6.1.b	2000	0	27329	.	.	1	1	1	0	0	0	0	0	0	0	0
	R1B	0	0	0	0	6.1.b	2000	0	27329	.	.	0	0	0	0	0	0	1	0	0	0	0
	R5C	0	0	0	0	6.1.b	2000	0	27329	.	.	0	0	1	0	0	0	0	0	0	0	0
M.2517	J5C	0	4	0	0	6.1.b	2001	0	1716410	.	.	0	1	1	0	0	0	0	0	0	0	1
M.2922	C2A	0	3	0	0	Art.6.2	2003	0	51 133	.	.	0	0	1	0	0	0	0	0	0	0	0
	C8A	0	0	0	0	Art.6.2	2003	0	51 133	1	1	1	1	1	0	0	0	0	0	0	0	0
	D4A	0	0	1	1	Art.6.2	2003	0	51 133	.	.	1	1	1	0	0	0	0	0	0	0	0
	G4B	13	0	0	0	Art.6.2	2003	0	51 133	1	1	1	1	1	0	0	0	0	0	0	0	1
	H2A	0	3	0	0	Art.6.2	2003	0	51 133	1	1	1	1	1	0	0	0	0	0	0	0	0
	J1F	1	0	0	0	Art.6.2	2003	0	51 133	.	.	.	.	1	0	0	0	0	0	0	0	0
	G4B	13	0	0	0	Art.6.2	2003	0	51 133	1	1	1	1	1	0	0	0	0	0	0	0	1
	A11F	0	0	0	0	Art.6.2	2004	0	28 070	0	.	0	0	1	0	0	0	0	0	0	0	0
	B1B	0	4	0	0	Art.6.2	2004	0	28 070	1	1	0	1	1	1	0	0	0	0	0	0	1
	B3X	12	0	0	0	Art.6.2	2004	0	28 070	0	.	0	1	0	0	0	0	0	1	0	0	1
	C1B	0	0	0	0	Art.6.2	2004	0	28 070	1	1	0	1	1	0	0	0	0	0	0	0	1
	C1F	0	0	0	0	Art.6.2	2004	0	28 070	1	1	0	0	1	0	0	0	0	0	0	0	0

M.3354	J1X	2	3	0	0	Art.6.2	2004	0	28 070	1	1	1	1	1	0	0	0	0	0	0	0	1
	M1C	0	0	0	0	Art.6.2	2004	0	28 070	1	1	0	0	1	0	0	0	0	0	0	0	0
	A7A	0	0	0	0	Art.6.2	2004	0	28 070	1	1	.	.	1	0	0	0	0	0	0	0	0
	C3A	0	6	0	0	Art.6.2	2004	0	28 070	1	1	.	.	1	0	0	0	0	0	0	0	0
	C4A	1	2	0	0	Art.6.2	2004	0	28 070	1	1	.	.	1	0	0	0	0	0	0	0	0
	C5B	0	0	0	0	Art.6.2	2004	0	28 070	1	1	.	.	1	0	0	0	0	0	0	0	0
	H2A	0	3	0	0	Art.6.2	2004	0	28 070	1	0	1	0	0	0	0	0	1	0	0	0	1
	J1D	8	2	0	0	Art.6.2	2004	0	28 070	1	1	1	1	1	0	0	0	0	0	0	0	0
	J1F	2	0	0	0	Art.6.2	2004	0	28 070	1	1	0	0	1	0	0	0	0	0	0	0	0
	M3B	3	0	0	0	Art.6.2	2004	0	28 070	1	1	1	1	1	0	0	0	0	0	0	0	0
	N2B	1	2	0	0	Art.6.2	2004	0	28 070	1	1	1	1	1	0	0	0	0	0	0	0	0
	N3A	13	0	0	0	Art.6.2	2004	0	28 070	1	0	1	0	0	1	0	0	0	0	0	0	1
	N5A	20	2	0	0	Art.6.2	2004	0	28 070	.	.	1	.	0	1	0	0	0	0	0	0	1
	N5B	0	5	0	0	Art.6.2	2004	0	28 070	1	1	1	1	1	0	0	0	0	0	0	0	0
	N7X	3	0	0	0	Art.6.2	2004	0	28 070	.	.	1	1	1	0	0	0	0	0	0	0	0
M.3544	A2A	0	7	1	1	6(2)	2004	1	29455	0	0	0	1	1	0	0	1	0	0	0	0	1
	N2B	1	2	1	0	6(2)	2004	1	29455	0	0	0	0	0	0	0	1	0	0	0	0	1
	D1A	1	3	1	0	6(2)	2004	1	29455	0	0	0	0	1	0	0	0	1	0	0	0	1
M.3751	A2B	17	5	1	1	6(2)	2005	1	.	1	1	0	0	1	0	0	1	0	0	0	0	1
	D6D	0	2	1	1	6(2)	2005	1	.	1	1	1	1	0	0	0	0	0	0	0	0	0
	H4A	0	0	0	0	6(2)	2005	1	.	1	0	0	0	0	1	0	0	0	0	0	0	0
	L4A	41	0	1	0	6(2)	2005	1	.	0	0	1	1	0	0	0	0	0	0	0	0	0
	M2A	0	0	1	1	6(2)	2005	1	.	0	0	1	1	0	0	0	1	0	0	0	0	0
	M3B	3	0	1	0	6(2)	2005	1	.	1	0	0	1	1	0	1	0	0	0	0	0	1
	M4A	1	0	1	0	6(2)	2005	1	.	0	0	1	0	1	1	1	0	0	0	0	0	1
	N5B	0	5	1	1	6(2)	2005	1	.	0	0	1	1	1	0	0	0	0	0	0	0	1
	N6A	28	6	1	1	6(2)	2005	1	.	1	1	1	1	0	0	0	0	0	1	0	0	0
	N6B	3	0	0	0	6(2)	2005	1	.	0	0	1	1	0	0	1	0	0	0	0	0	0
	R6A	10	0	1	1	6(2)	2005	1	.	0	0	0	0	1	0	0	0	0	0	0	0	0
	S1G	2	7	1	0	6(2)	2005	1	.	1	0	1	0	0	1	0	0	0	0	0	0	0
M.3853	A6A	1	6	1	0	6(1)(b)	2005	1	8472	0	0	1	1	0	0	0	1	0	0	0	0	0
	A9A	0	1	1	1	6(1)(b)	2005	1	8472	0	0	1	1	0	0	0	1	0	0	0	0	0
	C2A	0	3	1	0	6(1)(b)	2005	1	8472	0	0	1	1	0	0	0	0	0	0	0	0	0
	G3C	0	0	1	0	6(1)(b)	2005	1	8472	0	0	0	0	0	0	0	0	0	0	0	0	0
M.3928	L1C	10	0	1	0	6(1)(b)	2005	1	8472	1	1	0	0	1	0	0	0	0	0	0	0	0
	J1E	0	0	1	0	6(1)(b)	2005	1	5303	0	0	0	0	0	0	0	0	0	0	0	0	0
	R3A	9	4	1	0	6(1)(b)	2005	1	5303	0	0	0	0	0	0	0	0	0	0	0	0	0
	R3D	5	2	1	0	6(1)(b)	2005	1	5303	0	0	0	0	0	0	0	0	0	0	0	0	0
M.4007	D8A	0	2	1	0	6(1)(b)	2006	1	.	1	0	0	1	1	0	0	0	1	0	0	0	1
	R5A	0	0	1	0	6(1)(b)	2006	1	.	1	0	0	1	1	0	0	1	0	1	0	0	0
M.4049	J7A	5	9	1	0	6(1)(b)	2006	1	25800	0	0	0	1	1	0	0	0	0	0	0	0	1
	L4A	41	0	1	0	6(1)(b)	2006	1	25800	1	1	0	1	1	0	0	1	0	1	0	0	1
	J1K	0	0	1	0	6(1)(b)	2006	1	25800	0	0	0	1	1	0	0	0	0	0	0	0	1
M.4198	G1B	0	0	1	0	6(1)(b)	2006	1	32691	0	0	1	1	0	0	0	0	0	0	0	0	0
	C5A	0	2	1	0	6(1)(b)	2006	1	32691	0	0	1	1	0	0	0	0	0	0	0	0	0
	D1A	1	3	1	0	6(1)(b)	2006	1	32691	1	1	0	1	1	0	0	0	0	0	0	0	1
	D7B	0	4	1	0	6(1)(b)	2006	1	32691	0	0	1	1	1	0	0	0	0	0	0	0	0
	N5B	0	5	1	0	6(1)(b)	2006	1	32691	1	1	0	0	1	0	0	0	0	0	0	0	0
M.4314	D1A	1	3	1	0	6(2)	2006	1	43720	1	1	0	1	0	0	0	1	0	0	0	0	1
	R5A	0	0	1	0	6(2)	2006	1	43720	1	1	0	0	0	0	0	1	0	0	0	0	0
	C5A	0	2	1	0	6(2)	2006	1	43720	0	0	1	1	0	0	0	1	0	0	0	0	0
	N2B	1	2	1	0	6(2)	2006	1	43720	1	1	1	0	0	0	0	0	1	0	0	0	1
	A6A	1	5	1	0	6(2)	2006	1	43720	0	0	1	1	0	0	0	0	0	0	0	0	0
	A2A	0	7	1	0	6(2)	2006	1	43720	1	1	0	0	1	0	0	0	0	0	0	0	0

	R5D	1	2	1	0	6(2)	2006	1	43720	0	0	1	1	0	0	0	0	0	0	0	0	0
	S1G	2	7	1	0	6(2)	2006	1	43720	0	0	0	0	0	0	0	0	0	0	0	0	0
M.4402	R6A	10	0	1	0	6(1)(b)	2006	1	2500	1	1	1	1	0	0	0	1	0	0	0	0	0
	N3A	13	0	1	0	6(1)(b)	2006	1	2500	1	1	0	0	0	0	0	0	0	0	0	0	0
	C1D	0	0	1	0	6(1)(b)	2006	1	2500	1	1	0	0	0	0	0	0	0	0	0	0	0
	B3A	0	2	1	0	6(1)(b)	2006	1	2500	0	0	0	0	0	0	0	0	0	0	0	0	0
	R1B	0	0	1	0	6(1)(b)	2006	1	2500	0	0	0	0	0	0	0	0	0	0	0	0	0
	C4A	1	2	1	0	6(1)(b)	2006	1	2500	0	0	0	0	0	0	0	0	0	0	0	0	0
	R3F	0	2	1	0	6(1)(b)	2006	1	2500	0	0	0	0	0	0	0	0	0	0	0	0	0
M.4418	A2B	17	5	1	0	6(1)(b)	2006	1	.	1	1	0	0	0	1	0	0	0	0	0	0	1
M.5253	A2A	0	7	1	0	6(2)	2009	1	28652	1	1	1	0	1	0	0	0	0	0	0	0	1
	A3A	2	0	1	0	6(2)	2009	1	28652	0	0	1	1	1	0	0	0	0	0	0	0	0
	A4A	3	2	1	0	6(2)	2009	1	28652	0	0	0	1	1	0	0	1	0	0	0	0	1
	A5B	0	0	1	0	6(2)	2009	1	28652	0	0	1	1	1	0	0	0	0	0	0	0	0
	A7A	0	0	1	0	6(2)	2009	1	28652	0	0	1	1	0	0	0	0	0	0	0	0	0
	A12C	0	2	1	0	6(2)	2009	1	28652	0	0	1	1	0	0	0	0	0	0	0	0	0
	A10B	37	0	1	0	6(2)	2009	1	28652	1	0	1	0	1	0	0	0	0	0	0	0	1
	B1B	0	4	1	0	6(2)	2009	1	28652	1	0	0	1	0	1	0	0	1	1	0	0	1
	B1C	0	6	1	0	6(2)	2009	1	28652	0	0	1	0	1	1	0	0	0	0	1	0	1
	C4A	1	2	1	0	6(2)	2009	1	28652	0	0	1	0	0	0	0	1	0	0	0	0	1
	C7A	1	0	1	0	6(2)	2009	1	28652	0	0	1	1	0	0	0	0	0	0	0	0	0
	D1A	1	3	1	0	6(2)	2009	1	28652	1	1	0	1	1	1	0	0	0	0	0	0	1
	G4C	2	2	1	0	6(2)	2009	1	28652	0	0	1	0	0	0	0	1	0	0	0	0	1
	J1G	1	2	0	0	6(2)	2009	1	28652	1	0	1	0	0	0	0	0	1	1	0	1	1
	J4A	0	9	1	0	6(2)	2009	1	28652	1	1	0	0	0	0	1	0	0	1	0	0	2
	M1A	16	3	1	0	6(2)	2009	1	28652	1	0	1	0	0	0	0	0	0	0	0	0	1
	M5B	18	5	1	0	6(2)	2009	1	28652	0	0	1	1	1	0	0	0	0	0	0	0	0
	N2B	1	2	1	0	6(2)	2009	1	28652	1	0	1	0	0	0	0	1	0	0	0	0	1
	N5B	0	5	1	0	6(2)	2009	1	28652	1	0	0	0	1	0	0	1	0	0	0	0	1
	R6A	10	0	1	0	6(2)	2009	1	28652	1	0	0	0	0	0	0	0	0	0	0	0	0
M.5295	L1C	10	0	1	0	6(1)b and 6(	2008	1	8660	0	0	1	0	1	0	0	0	0	0	0	1	1
	V3D	0	0	1	0	6(1)b and 6(	2008	1	8660	0	0	1	0	1	0	0	0	0	0	0	0	1
	L1X	37	5	1	0	6(1)b and 6(	2008	1	8660	0	0	.	.	1	0	0	0	0	1	0	0	1
	L1B	9	0	1	0	6(1)b and 6(	2008	1	8660	0	0	.	.	1	0	0	0	0	1	0	0	1
	L2B	6	4	1	0	6(1)b and 6(	2008	1	8660	0	0	.	.	1	0	0	0	0	1	0	0	1
	A10B	37	0	1	0	6(1)b and 6(	2008	1	8660	1	1	1	1	.	.	.	.	.	.	.	.	.
	A11B	0	4	0	1	6(1)b and 6(	2008	1	8660	1	1	1	1	0	0	0	1	0	0	0	0	0
	A11C	0	3	1	0	6(1)b and 6(	2008	1	8660	0	0	.	.	1	0	0	0	0	0	0	0	.
	A11D	0	5	1	0	6(1)b and 6(	2008	1	8660	1	1	1	1	1	0	0	0	0	0	0	0	0
	A12A	0	0	1	0	6(1)b and 6(	2008	1	8660	0	0	1	1	1	0	0	0	0	0	0	0	0
	J1F	1	0	1	0	6(1)b and 6(	2008	1	8660	1	1	1	1	1	0	0	0	0	0	0	0	0
	N3A	13	0	1	0	6(1)b and 6(	2008	1	8660	1	1	1	1	0	0	0	0	0	0	0	0	.
	N5C	4	0	1	0	6(1)b and 6(	2008	1	8660	1	1	0	1	1	0	0	0	0	0	0	0	0
	N6A	28	6	1	0	6(1)b and 6(	2008	1	8660	0	0	0	0	1	0	0	0	0	0	0	0	0
M.5476	L1X	37	5	1	0	6(1)b and 6(	2009	1	48362	1	1	0		1	1		0	1	0	0	0	1
	J1C	3	2	1	0	6(1)b and 6(	2009	1	48362	1	1	0	0	.	.	.	.	.	.	.	.	0
	J1X	2	3	1	0	6(1)b and 6(	2009	1	48362	1	0	0	1	1	0	0	0	0	0	0	0	1
	N5C	4	0	1	0	6(1)b and 6(	2009	1	48362	1	1	1	1	1	0	0	0	0	0	0	0	0
	N6A	28	6	1	0	6(1)b and 6(	2009	1	48362	1	1	1	1	1	0	0	0	0	0	0	0	0
	N7D	0	2	1	0	6(1)b and 6(	2009	1	48362	.	.	.	.	.	.	.	.	.	.	.	.	.
	L4A	41	0	1	0	6(1)b and 6(	2009	1	48362	.	.	.	.	.	.	.	.	.	.	.	.	0
	R1A	2	8	1	0	6(1)b	2009	1	.	1	1	.	.	1	0	1	0	1	0	0	0	0
	R1B	0	0	1	0	6(1)b	2009	1	.	1	1	.	.	1	0	1	0	1	0	0	0	0
	R6A	10	0	1	0	6(1)b	2009	1	.	1	1	.	.	1	0	1	0	1	0	0	0	0

M.5502	R3J	0	2	1	0	6(1)b	2009	1	.	1	1	.	.	1	0	1	0	1	0	0	0	0
	J2A	6	0	1	0	6(1)b	2009	1	.	1	1	0	1	1	1	0	0	1	0	1	0	1
	N6A	28	6	1	0	6(1)b	2009	1	.	1	1	1	.	1	0	0	0	0	0	0	0	0
	H2A	0	3	1	0	6(1)b	2009	1	.	.	.	1	.	.	.	.	.	.	.	.	.	.
	M1A	16	3	1	0	6(1)b	2009	1	.	.	.	1	1	1	0	1	0	1	0	0	0	0
	H2A	0	3	1	0	6(1)b	2009	1	.	.	.	1	1	1	0	1	0	1	0	0	0	0
	L4A	41	0	1	0	6(1)b	2009	1	.	.	.	1	1	1	0	1	0	1	0	0	0	0
M.5530	D1A	1	3	1	0	6(1)b	2009	1	.	1	.	.	.	.	.	.	.	.	.	.	.	.
	D2A	0	0	1	0	6(1)b	2009	1	.	1	.	.	.	.	.	.	.	.	.	.	.	.
	D5A	1	0	1	0	6(1)b	2009	1	.	1	.	.	.	.	.	.	.	.	.	.	.	.
	D6D	0	2	1	0	6(1)b	2009	1	.	1	0	0	0	1	0	0	0	0	0	0	0	1
	D7A	0	0	1	0	6(1)b	2009	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.
M.5555	L1D	2	0	1	0	6(1)b	2009	1	.	1	1	1	1	0	0	1	0	0	0	0	0	1
	V3D	0	0	1	0	6(1)b	2009	1	.	1	1	.	.	0	0	1	0	0	0	0	0	1
	M5B	18	5	1	0	6(1)b	2009	1	.	1	.	1	.	1	0	0	0	1	0	0	0	.
M.5778	S1A	2	0	1	0	6(1)b	2010	1	36000	.	.	1	1	1	0	0	0	0	0	0	0	0
	S1B	2	0	1	0	6(1)b	2010	1	36000	.	.	1	1	1	0	0	0	0	0	0	0	0
	S1C	0	3	1	0	6(1)b	2010	1	36000	.	.	0	0	1	0	0	0	0	0	0	0	0
	S1R	0	0	1	0	6(1)b	2010	1	36000	.	.	1	1	1	0	0	0	0	0	0	0	0
	S1E	7	2	1	0	6(1)b	2010	1	36000	.	.	1	1	1	0	1	0	0	0	0	0	2
	S1G	2	7	1	0	6(1)b	2010	1	36000	1	0	.	.	1	1	1	1	0	0	0	0	1
	S1F	0	0	0	0	6(1)b	2010	1	36000	.	.	0	1	1	0	1	0	0	1	0	0	2
	S1L	3	0	1	0	6(1)b	2010	1	36000	.	.	0	1	1	0	0	0	0	0	0	0	1
	S1M	0	0	0	1	6(1)b	2010	1	36000	.	.	0	.	0	0	0	1	0	0	0	0	0
M.5865	A5A	1	2	1	1	6(2) and 6(1	2010	1	11628	1	0	0	1	1	0	1	0	1	0	0	0	2
	A11D	0	5	1	0	6(2) and 6(1	2010	1	11628	1	.	1	.	0	0	0	0	0	0	0	0	.
	A11G	0	2	1	0	6(2) and 6(1	2010	1	11628	.	.	1	.	0	0	0	0	0	0	0	0	.
	A11X	0	4	1	0	6(2) and 6(1	2010	1	11628	1	1	.	.	1	0	0	0	0	0	0	0	2
	B3X	11	0	1	0	6(2) and 6(1	2010	1	11628	.	.	.	.	0	0	0	1	0	0	0	0	1
	C2A	0	3	1	0	6(2) and 6(1	2010	1	11628	.	.	.	.	1	0	0	0	0	0	0	0	1
	C3A	0	6	1	0	6(2) and 6(1	2010	1	11628	.	.	.	.	1	0	0	0	0	0	0	0	1
	H2A	0	3	1	0	6(2) and 6(1	2010	1	11628	.	.	0	1	1	0	0	0	0	0	0	0	1
	H3B	0	0	1	0	6(2) and 6(1	2010	1	11628	.	.	.	.	0	1	1	0	0	0	0	0	1
	J1F	1	0	1	0	6(2) and 6(1	2010	1	11628	.	.	.	.	.	.	.	.	.	.	.	.	.
	J4A	0	9	1	0	6(2) and 6(1	2010	1	11628	.	.	.	.	1	0	0	0	0	0	0	0	1
	L1X	37	5	1	0	6(2) and 6(1	2010	1	11628	1	1	.	.	1	0	0	0	0	0	0	0	1
	L2B	6	4	1	0	6(2) and 6(1	2010	1	11628	1	0	.	.	1	0	0	0	0	0	0	0	1
	L3A	23	2	1	0	6(2) and 6(1	2010	1	11628	.	.	0	1	1	0	0	0	0	0	0	0	1
	L4B	0	0	1	0	6(2) and 6(1	2010	1	11628	1	1	.	.	.	.	.	.	.	.	.	.	.
	L4X	0	0	1	0	6(2) and 6(1	2010	1	11628	1	1	.	.	.	.	.	.	.	.	.	.	.
	M1A	16	3	1	0	6(2) and 6(1	2010	1	11628	1	1	.	.	1	0	0	0	1	0	0	0	1
	M4A	1	0	1	0	6(2) and 6(1	2010	1	11628	.	.	.	.	0	0	1	0	0	0	0	0	2
	N2A	3	0	1	0	6(2) and 6(1	2010	1	11628	.	.	.	.	0	0	0	0	1	0	0	0	2
	N2B	1	2	1	0	6(2) and 6(1	2010	1	11628	1	0	.	.	1	0	0	0	1	0	0	0	1
	N3A	13	0	1	0	6(2) and 6(1	2010	1	11628	1	.	.	.	.	.	.	.	.	.	.	.	.
	N5A	21	2	1	0	6(2) and 6(1	2010	1	11628	1	.	.	.	.	.	.	.	.	.	.	.	.
	N5B	0	5	1	0	6(2) and 6(1	2010	1	11628	1	1	.	.	1	0	1	0	0	0	0	0	1
	N6A	28	6	1	0	6(2) and 6(1	2010	1	11628	0	0	.	.	0	1	1	0	0	0	0	0	2
	R3C	0	2	1	0	6(2) and 6(1	2010	1	11628	1	1	1	1	1	0	0	0	0	0	0	0	0
	R3D	5	2	1	0	6(2) and 6(1	2010	1	11628	0	0	1	0	1	0	0	0	0	0	0	0	2
	R5C	0	0	1	0	6(2) and 6(1	2010	1	11628	0	0	1	1	1	0	0	0	1	0	0	0	0
	R6A	10		1	0	6(2) and 6(1	2010	1	11628	1	1	1	1	1	0	1	0	0	0	0	0	0
	S1F	0	0	1	0	6(2) and 6(1	2010	1	11628	0	0	1	0	1	0	0	0	1	0	0	0	2
	N2B	1	2	1	0	6(2) and 6(1	2010	1	9 612	1	1	.	.	1	0	0	0	0	0	0	0	0

M.5953	A1A	0	5	1	0	6(2) and 6(1	2010	1	9 612	1	0	0	1	1	0	0	0	0	0	0	0	1
	R2A	0	0	1	0	6(2) and 6(1	2010	1	9 612	1	1	1	1	1	0	0	0	0	0	0	1	0
	A2A	0	7	1	0	6(2) and 6(1	2010	1	9 612	1	-	0	-	-	-	-	-	-	-	-	-	-
	D4A	0	0	0	1	6(2) and 6(1	2010	1	9 612	1	1	1	1	1	0	0	0	0	0	0	0	0

Annex 2:

```
Results 1989-2011_2  Saturday May 17 16:31:47 2014   Page 1
```

```
      name:  <unnamed>
       log:  C:\Users\Marie\Desktop\Stata_2014\1989_2011\Results_1989_2011.smcl
  log type:  smcl
 opened on:  21 Apr 2014, 12:12:53

 1 . do "C:\Users\Marie\Desktop\Stata_2014\1989_2011\All_Data_Do_File_new.do"

 2 . * MARKET DEFINITION FOR PHARMACEUTICALS - MERGERS 1989-2011*
 3 .
 4 .
 5 . use "C:\Users\Marie\Desktop\Stata_2014\1989_2011\All_data1989_2011.dta", clear

 6 .
 7 . *1 Description and summary of the statistics from 1989-2011 *
 8 .
 9 . describe marketresult atc3_ema atc4classes turnover mergreg iudg eff ai otc galform channel
   > m ecoreg supplys

              storage  display     value
variable name   type   format      label      variable label
------------------------------------------------------------------------------
marketresult    byte   %8.0g
atc3_ema        byte   %8.0g                 ATC3_EMA
atc4classes     byte   %8.0g                 ATC4classes
turnover        long   %12.0g                Turn-over
mergreg         byte   %8.0g                 MergReg
iudg            byte   %8.0g                 IUDG
eff             byte   %8.0g                 EFF
ai              byte   %8.0g                 AI
otc             byte   %8.0g                 OTC
galform         byte   %8.0g                 Galform
channelm        byte   %8.0g                 Channelm
ecoreg          byte   %8.0g                 EcoReg
supplys         byte   %8.0g                 SupplyS

10 .
11 . summarize marketresult atc3_ema atc4classes turnover mergreg iudg eff ai otc galform channe
   > lm ecoreg supplys

    Variable |        Obs        Mean    Std. Dev.       Min        Max
-------------+---------------------------------------------------------
marketresult |        199    .3869347    .4882769          0          1
    atc3_ema |        217    5.018433    9.404965          0         41
 atc4classes |        216       2.125    2.379784          0          9
    turnover |        144    33532.56    141791.4       2500    1716410
     mergreg |        217    .6958525    .4611091          0          1
-------------+---------------------------------------------------------
        iudg |        202    .6980198    .4602574          0          1
         eff |        202    .0792079     .270734          0          1
          ai |        201    .1094527    .3129859          0          1
         otc |        202    .1039604    .3059674          0          1
     galform |        202    .1188119    .3243709          0          1
-------------+---------------------------------------------------------
    channelm |        202    .0594059    .2369702          0          1
      ecoreg |        202     .019802    .1396654          0          1
     supplys |        202    .0247525    .1557559          0          1

12 .
13 . *2 Logit model and comparing the performance of different models*
```

```
14 .
15 . *Model 0*
16 .
17 . logit marketresult atc3_ema atc4classes mergreg turnover iudg eff ai otc galform channelm e
   > coreg supplys

   note: eff != 0 predicts success perfectly
         eff dropped and 7 obs not used

   note: ai != 0 predicts success perfectly
         ai dropped and 6 obs not used

   note: channelm != 0 predicts success perfectly
         channelm dropped and 5 obs not used

   note: supplys != 0 predicts success perfectly
         supplys dropped and 1 obs not used

   note: ecoreg omitted because of collinearity
   Iteration 0:   log likelihood = -70.245338
   Iteration 1:   log likelihood =  -46.67591
   Iteration 2:   log likelihood = -45.784467
   Iteration 3:   log likelihood = -45.774028
   Iteration 4:   log likelihood = -45.774018
   Iteration 5:   log likelihood = -45.774018

   Logistic regression                               Number of obs   =        110
                                                     LR chi2(7)      =      48.94
                                                     Prob > chi2     =     0.0000
   Log likelihood = -45.774018                       Pseudo R2       =     0.3484

   ------------------------------------------------------------------------------
   marketresult |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
   -------------+----------------------------------------------------------------
      atc3_ema |   .0244918   .0317789     0.77   0.441    -.0377937    .0867772
    atc4classes |    .282979   .1103669     2.56   0.010     .0666638    .4992942
       mergreg |   2.398061   .8272585     2.90   0.004      .776664    4.019458
      turnover |   3.60e-06   3.82e-06     0.94   0.346    -3.88e-06    .0000111
          iudg |   2.116146   .8212852     2.58   0.010     .5064567    3.725836
           eff |          0  (omitted)
            ai |          0  (omitted)
           otc |   2.872588   .9336822     3.08   0.002     1.042604    4.702571
       galform |   3.374537   1.223657     2.76   0.006     .9762124    5.772861
      channelm |          0  (omitted)
        ecoreg |          0  (omitted)
       supplys |          0  (omitted)
         _cons |  -5.720983   1.169961    -4.89   0.000    -8.014065   -3.427901
   ------------------------------------------------------------------------------

18 . test atc3_ema turnover

    ( 1)  [marketresult]atc3_ema = 0
    ( 2)  [marketresult]turnover = 0

              chi2(  2) =    1.43
            Prob > chi2 =    0.4883

19 .
20 . *Model 1*
21 .
```

```
22 . logit marketresult atc4classes mergreg iudg eff ai otc galform channelm ecoreg supplys

Iteration 0:   log likelihood = -130.38348
Iteration 1:   log likelihood = -103.32905
Iteration 2:   log likelihood = -103.11307
Iteration 3:   log likelihood =  -103.1128
Iteration 4:   log likelihood =  -103.1128

Logistic regression                               Number of obs   =        195
                                                  LR chi2(10)     =      54.54
                                                  Prob > chi2     =     0.0000
Log likelihood =  -103.1128                       Pseudo R2       =     0.2092

------------------------------------------------------------------------------
marketresult |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 atc4classes |   .1487621   .0737348     2.02   0.044     .0042445    .2932797
     mergreg |    1.18055    .427446     2.76   0.006     .3427716    2.018329
        iudg |   .8353235   .4451743     1.88   0.061    -.0372022    1.707849
         eff |   3.000584   .9048418     3.32   0.001     1.227127    4.774041
          ai |   .3839894   .6125324     0.63   0.531     -.816552    1.584531
         otc |   1.356861   .5968081     2.27   0.023      .187139    2.526584
     galform |   .6790351   .5760048     1.18   0.238    -.4499135    1.807984
    channelm |   1.991945   .8966222     2.22   0.026     .2345975    3.749292
      ecoreg |  -.9395471   1.785588    -0.53   0.599    -4.439235    2.560141
     supplys |   .5734383   1.229868     0.47   0.641    -1.837059    2.983936
       _cons |  -2.784959   .5410838    -5.15   0.000    -3.845464   -1.724454
------------------------------------------------------------------------------

23 .
24 . dlogit2 marketresult atc4classes mergreg iudg eff ai otc galform channelm ecoreg supplys

Marginal effects from logit                       Number of obs   =        195
                                                  chi2(10)        =      34.06
                                                  Prob > chi2     =     0.0002
Log Likelihood =  -103.1128                       Pseudo R2       =     0.2092

------------------------------------------------------------------------------
marketresult |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 atc4classes |   .0350966   .0173873     2.02   0.044     .0010181     .069175
     mergreg |   .2785202   .0997596     2.79   0.005     .0829949    .4740455
        iudg |   .1970729   .1053324     1.87   0.061    -.0093748    .4035206
         eff |   .7079098   .2188648     3.23   0.001     .2789427    1.136877
          ai |   .0905923   .1446514     0.63   0.531    -.1929191    .3741038
         otc |   .3201162    .141443     2.26   0.024     .0428931    .5973393
     galform |   .1602007   .1359556     1.18   0.239    -.1062674    .4266688
    channelm |   .4699476   .2147781     2.19   0.029     .0489903    .8909049
      ecoreg |  -.2216617   .4209504    -0.53   0.598    -1.046709    .6033859
     supplys |   .1352879   .2901562     0.47   0.641    -.4334079    .7039836
       _cons |  -.6570388   .1196109    -5.49   0.000    -.8914718   -.4226058
------------------------------------------------------------------------------

Marginal effects evaluated at

   atc4classes      mergreg         iudg          eff           ai          otc      galform
>     channelm       ecoreg      supplys
x     2.153846     .6615385     .7025641     .0769231     .1076923     .1076923     .1128205
>     .0615385     .0205128      .025641

         _cons
x            1
```

```
. 
. *Model 2*
. 
. logit marketresult mergreg iudg eff ai otc galform channelm ecoreg

Iteration 0:   log likelihood = -130.87573
Iteration 1:   log likelihood = -106.05364
Iteration 2:   log likelihood = -105.85586
Iteration 3:   log likelihood = -105.85568
Iteration 4:   log likelihood = -105.85568

Logistic regression                               Number of obs   =        196
                                                  LR chi2(8)      =      50.04
                                                  Prob > chi2     =     0.0000
Log likelihood = -105.85568                       Pseudo R2       =     0.1912

------------------------------------------------------------------------------
 marketresult |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
--------------+---------------------------------------------------------------
     mergreg |   1.300345   .4218178     3.08   0.002     .4735978    2.127093
        iudg |   .9762509   .4335547     2.25   0.024     .1264994    1.826002
         eff |   3.091924   .8856797     3.49   0.000     1.356024    4.827825
          ai |   .1685939   .5765154     0.29   0.770    -.9613557    1.298543
         otc |   1.368968   .5868941     2.33   0.020     .2186767    2.519259
    galform |   .6502806   .5649972     1.15   0.250    -.4570935    1.757655
   channelm |   2.188888   .8886737     2.46   0.014     .4471196    3.930656
     ecoreg |  -.6874328   1.832277    -0.38   0.708    -4.278631    2.903765
      _cons |  -2.625948   .5308504    -4.95   0.000    -3.666396   -1.585501
------------------------------------------------------------------------------

. 
. dlogit2 marketresult mergreg iudg eff ai otc galform channelm ecoreg

Marginal effects from logit                       Number of obs   =        196
                                                  chi2(8)         =      31.08
                                                  Prob > chi2     =     0.0001
Log Likelihood = -105.85568                       Pseudo R2       =     0.1912

------------------------------------------------------------------------------
 marketresult |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
--------------+---------------------------------------------------------------
     mergreg |   .3069916   .0983248     3.12   0.002     .1142786    .4997045
        iudg |   .2304778   .1028214     2.24   0.025     .0289516    .4320041
         eff |   .7299558   .2146771     3.40   0.001     .3091964    1.150715
          ai |   .0398024    .136131     0.29   0.770    -.2270095    .3066143
         otc |   .3231923   .1393417     2.32   0.020     .0500875    .5962971
    galform |   .1535213   .1335632     1.15   0.250    -.1082578    .4153004
   channelm |   .5167628   .2133821     2.42   0.015     .0985416     .934984
     ecoreg |  -.1622923   .4320897    -0.38   0.707    -1.009173     .684588
      _cons |   -.619946   .1180873    -5.25   0.000    -.8513929   -.3884991
------------------------------------------------------------------------------
Marginal effects evaluated at

    mergreg      iudg       eff        ai       otc   galform  channelm    ecoreg     _cons
x  .6632653  .7040816  .0765306  .1122449  .1071429  .1122449  .0612245  .0204082         1

. 
. 
. * Comparison of the predicted outcomes with the actual outcomes
. 
```

```
35 . *Comparison for model 1*
36 .
37 . quietly logistic marketresult atc4classes mergreg iudg eff ai otc galform channelm ecoreg s
   > upplys

38 . estat classification
```

Logistic model for marketresult

Classified	True D	True ~D	Total
+	**40**	**17**	**57**
-	**36**	**102**	**138**
Total	**76**	**119**	**195**

Classified + if predicted Pr(D) >= .5
True D defined as marketresult != 0

Sensitivity	Pr(+| D)	**52.63%**
Specificity	Pr(-|~D)	**85.71%**
Positive predictive value	Pr(D| +)	**70.18%**
Negative predictive value	Pr(~D| -)	**73.91%**
False + rate for true ~D	Pr(+|~D)	**14.29%**
False - rate for true D	Pr(-| D)	**47.37%**
False + rate for classified +	Pr(~D| +)	**29.82%**
False - rate for classified -	Pr(D| -)	**26.09%**
Correctly classified		**72.82%**

```
39 . estat gof, group (10)
```

Logistic model for marketresult, goodness-of-fit test

(Table collapsed on quantiles of estimated probabilities)

```
      number of observations =       195
            number of groups =        10
  Hosmer-Lemeshow chi2(8) =         8.67
              Prob > chi2 =         0.3705

40 .
41 . *Comparison for model 2*
42 .
43 . quietly logistic marketresult mergreg iudg eff ai otc galform channelm ecoreg

44 . estat classification
```

Logistic model for marketresult

Classified	True D	True ~D	Total
+	**37**	**19**	**56**
-	**39**	**101**	**140**
Total	**76**	**120**	**196**

Classified + if predicted Pr(D) >= .5
True D defined as marketresult != 0

Sensitivity	Pr(+| D)	**48.68%**
Specificity	Pr(-|~D)	**84.17%**
Positive predictive value	Pr(D| +)	**66.07%**
Negative predictive value	Pr(~D| -)	**72.14%**
False + rate for true ~D	Pr(+|~D)	**15.83%**
False - rate for true D	Pr(-| D)	**51.32%**
False + rate for classified +	Pr(~D| +)	**33.93%**
False - rate for classified -	Pr(D| -)	**27.86%**
Correctly classified		**70.41%**

```
45 . estat gof, group (10)
```

Logistic model for marketresult, goodness-of-fit test

(Table collapsed on quantiles of estimated probabilities)
(There are only 7 distinct quantiles because of ties)

```
      number of observations =       196
            number of groups =         7
          Hosmer-Lemeshow chi2(5) =        11.50
                      Prob > chi2 =         0.0423
```

```
46 .
47 . *3 Calculate the fitted probabilities *
48 .
49 . *Impact of merger regulation*
50 .
51 . quietly logistic marketresult atc4classes mergreg iudg eff ai otc galform channelm ecoreg s
   > upplys

52 . prvalue, x(mergreg=0 iudg=0 eff=0 ai=0 otc=0 galform=0 channelm=0 ecoreg=0 supplys=0) rest(
   > mean)save
```

logistic: Predictions for **marketresult**

Confidence intervals by delta method

		95% Conf. Interval	
Pr(y=1|x):	**0.0784**	[**0.0024**,	**0.1544**]
Pr(y=0|x):	**0.9216**	[**0.8456**,	**0.9976**]

	atc4classes	mergreg	iudg	eff	ai	otc	galform
>	channelm	ecoreg	supplys				
x=	**2.1538462**	**0**	**0**	**0**	**0**	**0**	**0**
>	**0**	**0**	**0**				

```
53 . prvalue, x(mergreg=1) dif
```

logistic: Change in Predictions for **marketresult**

Confidence intervals by delta method

	Current	Saved	Change	95% CI for Change	
Pr(y=1|x):	**0.4790**	**0.0784**	**0.4006**	[**0.2648**,	**0.5364**]
Pr(y=0|x):	**0.5210**	**0.9216**	**-0.4006**	[**-0.5364**,	**-0.2648**]

	atc4classes	mergreg	iudg	eff	ai	otc	g
> alform	channelm	ecoreg	supplys				
Current=	**2.1538462**	**1**	**.7025641**	**.07692308**	**.10769231**	**.10769231**	**.11**
> **282051**	**.06153846**	**.02051282**	**.02564103**				
Saved=	**2.1538462**	**0**	**0**	**0**	**0**	**0**	
> **0**	**0**	**0**	**0**				
Diff=	**0**	**1**	**.7025641**	**.07692308**	**.10769231**	**.10769231**	**.11**
> **282051**	**.06153846**	**.02051282**	**.02564103**				

```
54 .
55 . *Impact of efficacy*
56 .
57 . quietly logistic marketresult atc4classes mergreg iudg eff ai otc galform channelm ecoreg s
   > upplys

58 . prvalue, x(mergreg=0 iudg=0 eff=1 ai=0 otc=0 galform=0 channelm=0 ecoreg=0 supplys=0) rest(
   > mean)

   logistic: Predictions for marketresult

   Confidence intervals by delta method

                                 95% Conf. Interval
     Pr(y=1|x):          0.6309   [ 0.2232,    1.0386]
     Pr(y=0|x):          0.3691   [-0.0386,    0.7768]

        atc4classes      mergreg         iudg          eff           ai          otc      galform
   >       channelm       ecoreg      supplys
   x=     2.1538462            0            0            1            0            0            0
   >             0            0            0

59 .
60 .
61 . *Impact of galenic form*
62 .
63 . quietly logistic marketresult atc4classes mergreg iudg eff ai otc galform channelm ecoreg s
   > upplys

64 . prvalue, x(mergreg=0 iudg=0 eff=0 ai=0 otc=0 galform=1 channelm=0 ecoreg=0 supplys=0) rest(
   > mean)

   logistic: Predictions for marketresult

   Confidence intervals by delta method

                                 95% Conf. Interval
     Pr(y=1|x):          0.1436   [-0.0473,    0.3346]
     Pr(y=0|x):          0.8564   [ 0.6654,    1.0473]

        atc4classes      mergreg         iudg          eff           ai          otc      galform
   >       channelm       ecoreg      supplys
   x=     2.1538462            0            0            0            0            0            1
   >             0            0            0

65 .
66 . *Impact of channel mode*
67 .
68 . quietly logistic marketresult atc4classes mergreg iudg eff ai otc galform channelm ecoreg s
   > upplys

69 . prvalue, x(mergreg=0 iudg=0 eff=0 ai=0 otc=0 galform=0 channelm=1 ecoreg=0 supplys=0) rest(
   > mean)

   logistic: Predictions for marketresult

   Confidence intervals by delta method

                                 95% Conf. Interval
     Pr(y=1|x):          0.3840   [-0.0729,    0.8409]
     Pr(y=0|x):          0.6160   [ 0.1591,    1.0729]

        atc4classes      mergreg         iudg          eff           ai          otc      galform
   >       channelm       ecoreg      supplys
   x=     2.1538462            0            0            0            0            0            0
   >             1            0            0
```

```
70 .
71 .
72 . *Impact of intended use, and in combination with change in merger regulation*
73 .
74 . quietly logistic marketresult atc4classes mergreg iudg eff ai otc galform channelm ecoreg s
   > upplys

75 . prvalue, x(mergreg=0 iudg=1 eff=0 ai=0 otc=0 galform=0 channelm=0 ecoreg=0 supplys=0) rest(
   > mean)

   logistic: Predictions for marketresult

   Confidence intervals by delta method

                                 95% Conf. Interval
     Pr(y=1|x):          0.1639   [ 0.0712,    0.2567]
     Pr(y=0|x):          0.8361   [ 0.7433,    0.9288]

        atc4classes      mergreg         iudg          eff           ai          otc      galform
   >       channelm       ecoreg      supplys
   x=     2.1538462            0            1            0            0            0            0
   >              0            0            0

76 .
77 . quietly logistic marketresult atc4classes mergreg iudg eff ai otc galform channelm ecoreg s
   > upplys

78 . prvalue, x(mergreg=1 iudg=1 eff=0 ai=0 otc=0 galform=0 channelm=0 ecoreg=0 supplys=0) rest(
   > mean)

   logistic: Predictions for marketresult

   Confidence intervals by delta method

                                 95% Conf. Interval
     Pr(y=1|x):          0.3897   [ 0.2563,    0.5230]
     Pr(y=0|x):          0.6103   [ 0.4770,    0.7437]

        atc4classes      mergreg         iudg          eff           ai          otc      galform
   >       channelm       ecoreg      supplys
   x=     2.1538462            1            1            0            0            0            0
   >              0            0            0

79 .
80 . *Impact of OTC, and in combination with change in merger regulation*
81 .
82 . quietly logistic marketresult atc4classes mergreg iudg eff ai otc galform channelm ecoreg s
   > upplys

83 . prvalue, x(mergreg=0 iudg=0 eff=0 ai=0 otc=1 galform=0 channelm=0 ecoreg=0 supplys=0) rest(
   > mean)

   logistic: Predictions for marketresult

   Confidence intervals by delta method

                                 95% Conf. Interval
     Pr(y=1|x):          0.2483   [ 0.0051,    0.4915]
     Pr(y=0|x):          0.7517   [ 0.5085,    0.9949]

        atc4classes      mergreg         iudg          eff           ai          otc      galform
   >       channelm       ecoreg      supplys
   x=     2.1538462            0            0            0            0            1            0
   >              0            0            0
```

```
84 .
85 . quietly logistic marketresult atc4classes mergreg iudg eff ai otc galform channelm ecoreg s
   > upplys

86 . prvalue, x(mergreg=1 iudg=0 eff=0 ai=0 otc=1 galform=0 channelm=0 ecoreg=0 supplys=0) rest(
   > mean)

   logistic: Predictions for marketresult

   Confidence intervals by delta method

                                 95% Conf. Interval
     Pr(y=1|x):          0.5182   [ 0.2767,    0.7597]
     Pr(y=0|x):          0.4818   [ 0.2403,    0.7233]

        atc4classes      mergreg         iudg          eff           ai          otc      galform
   >       channelm       ecoreg      supplys
   x=     2.1538462            1            0            0            0            1            0
   >              0            0            0

87 .
88 .
89 .
90 .
91 .
92 .
93 .
94 .
95 .
96 .
97 .
98 .
   end of do-file

99 . log close
         name:  <unnamed>
          log:  C:\Users\Marie\Desktop\Stata_2014\1989_2011\Results_1989_2011.smcl
     log type:  smcl
    closed on:  21 Apr 2014, 12:13:48
-------------------------------------------------------------------------------
```

Annex 3

```
Results 2004-2011_NEW  Sunday May 18 16:37:59 2014   Page 1
```

```
      name:  <unnamed>
       log:  C:\Users\Marie\Desktop\Stata_2014\2004_2011\Results_2004_2011_NEW.smcl
  log type:  smcl
 opened on:  18 May 2014, 16:36:31

 1 . do "C:\Users\Marie\Desktop\Stata_2014\2004_2011\All_Data_2004_2011_Do_File _NEW.do"

 2 . * MARKET DEFINITION FOR PHARMACEUTICALS - MERGERS 2004-2011*
 3 .
 4 .
 5 .
 6 . use "C:\Users\Marie\Desktop\Stata_2014\2004_2011\Data_2004_2011_korr.dta", clear

 7 .
 8 . *1 Description and summary of statistics from 2004-2011 *
 9 .
10 . label variable marketresult "scope of the relevant market"

11 .
12 . tabulate marketresult
```

scope of the relevant market	Freq.	Percent	Cum.
0	70	52.63	52.63
1	53	39.85	92.48
2	10	7.52	100.00
Total	133	100.00	

```
13 .
14 . describe marketresult atc4classes iudg eff ai otc galform channelm ecoreg supplys
```

variable name	storage type	display format	value label	variable label
marketresult	byte	%8.0g		**scope of the relevant market**
atc4classes	byte	%8.0g		**ATC4classes**
iudg	byte	%8.0g		**IUDG**
eff	byte	%8.0g		**EFF**
ai	byte	%8.0g		**AI**
otc	byte	%8.0g		**OTC**
galform	byte	%8.0g		**Galform**
channelm	byte	%8.0g		**Channelm**
ecoreg	byte	%8.0g		**EcoReg**
supplys	byte	%8.0g		**SupplyS**

```
15 .
16 . summarize marketresult atc4classes iudg eff ai otc galform channelm ecoreg supplys
```

Variable	Obs	Mean	Std. Dev.	Min	Max
marketresult	133	.5488722	.6332476	0	2
atc4classes	150	2.293333	2.459188	0	9
iudg	136	.5955882	.4925922	0	1
eff	136	.0882353	.2846854	0	1
ai	136	.1617647	.3695961	0	1
otc	136	.1544118	.3626788	0	1
galform	136	.1544118	.3626788	0	1
channelm	136	.0735294	.2619684	0	1
ecoreg	136	.0147059	.1208178	0	1
supplys	136	.0220588	.1474179	0	1

```
17 .
18 .
19 . *2 Study of the criteria for market definition in an ordered logit model from 2004-2011 as
   > data are naturally ordered*
20 .
21 . *Model 1*
22 . ologit marketresult atc4classes iudg eff ai otc galform channelm ecoreg supplys

Iteration 0:   log likelihood = -117.61375
Iteration 1:   log likelihood = -105.53737
Iteration 2:   log likelihood = -105.29332
Iteration 3:   log likelihood =  -105.2926
Iteration 4:   log likelihood =  -105.2926

Ordered logistic regression                     Number of obs   =        130
                                                LR chi2(9)      =      24.64
                                                Prob > chi2     =     0.0034
Log likelihood =  -105.2926                     Pseudo R2       =     0.1048

------------------------------------------------------------------------------
 marketresult |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
--------------+---------------------------------------------------------------
  atc4classes |   .1173108   .0738611     1.59   0.112    -.0274543    .2620758
         iudg |   .8910292   .4065028     2.19   0.028     .0942985     1.68776
          eff |   .9738386   .6627871     1.47   0.142    -.3252002    2.272877
           ai |   1.203347   .5444928     2.21   0.027     .1361612    2.270534
          otc |   .7003972   .5035318     1.39   0.164    -.2865071    1.687302
     galform |   .1537043   .5482155     0.28   0.779    -.9207784    1.228187
    channelm |   1.403255   .6613874     2.12   0.034     .1069591     2.69955
      ecoreg |   .5306228   1.434315     0.37   0.711    -2.280583    3.341829
     supplys |   .6509984   1.124704     0.58   0.563     -1.55338    2.855377
-------------+---------------------------------------------------------------
       /cut1 |    1.42736   .4040847                      .635369    2.219352
       /cut2 |    4.22119   .5669559                     3.109977    5.332403
------------------------------------------------------------------------------

23 .
24 . test supplys ecoreg

 ( 1)  [marketresult]supplys = 0
 ( 2)  [marketresult]ecoreg = 0

           chi2(  2) =    0.46
         Prob > chi2 =    0.7935

25 .
26 .
27 . *Model 2*
28 . ologit marketresult atc4classes iudg eff ai otc galform channelm

Iteration 0:   log likelihood = -117.61375
Iteration 1:   log likelihood = -105.75452
Iteration 2:   log likelihood = -105.52293
Iteration 3:   log likelihood = -105.52225
Iteration 4:   log likelihood = -105.52225

Ordered logistic regression                     Number of obs   =        130
                                                LR chi2(7)      =      24.18
                                                Prob > chi2     =     0.0011
Log likelihood = -105.52225                     Pseudo R2       =     0.1028
```

marketresult	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
atc4classes	.1105562	.0731059	1.51	0.130	-.0327287	.2538411
iudg	.9059951	.4021175	2.25	0.024	.1178593	1.694131
eff	1.05893	.6001935	1.76	0.078	-.1174274	2.235288
ai	1.136674	.533286	2.13	0.033	.0914525	2.181895
otc	.6784261	.5018017	1.35	0.176	-.3050872	1.661939
galform	.2085023	.5398536	0.39	0.699	-.8495912	1.266596
channelm	1.451722	.6527226	2.22	0.026	.1724093	2.731035
/cut1	1.399584	.3973106			.6208698	2.178299
/cut2	4.186829	.5616923			3.085932	5.287725

```
29 .
30 .
31 . *Model 3*
32 . ologit marketresult iudg eff ai otc galform channelm

Iteration 0:   log likelihood =   -118.273
Iteration 1:   log likelihood =  -107.9843
Iteration 2:   log likelihood = -107.82616
Iteration 3:   log likelihood = -107.82567
Iteration 4:   log likelihood = -107.82567

Ordered logistic regression                     Number of obs   =        131
                                                LR chi2(6)      =      20.89
                                                Prob > chi2     =     0.0019
Log likelihood = -107.82567                     Pseudo R2       =     0.0883
```

marketresult	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
iudg	.9685758	.3947838	2.45	0.014	.1948139	1.742338
eff	1.229691	.5897281	2.09	0.037	.0738449	2.385536
ai	.8959436	.5144725	1.74	0.082	-.1124041	1.904291
otc	.7164931	.4970344	1.44	0.149	-.2576763	1.690663
galform	.2136259	.5285154	0.40	0.686	-.8222452	1.249497
channelm	1.503687	.6573012	2.29	0.022	.2154005	2.791974
/cut1	1.185036	.3663527			.466998	1.903074
/cut2	3.912967	.5272063			2.879662	4.946273

```
33 .
34 .
35 .
36 . *3
37 .
38 . **Analysis with MODEL 2**
39 .
40 . **Part a.  Replicate ologit's results by using the pl and lrforce parameter
41 .
42 .
43 . gologit2 marketresult atc4classes iudg eff ai otc galform channelm, pl lrforce store(constr
   > ained)

Generalized Ordered Logit Estimates             Number of obs   =        130
                                                LR chi2(7)      =      24.18
                                                Prob > chi2     =     0.0011
Log likelihood = -105.52225                     Pseudo R2       =     0.1028
```

```
 ( 1)  [0]atc4classes - [1]atc4classes = 0
 ( 2)  [0]iudg - [1]iudg = 0
 ( 3)  [0]eff - [1]eff = 0
 ( 4)  [0]ai - [1]ai = 0
 ( 5)  [0]otc - [1]otc = 0
 ( 6)  [0]galform - [1]galform = 0
 ( 7)  [0]channelm - [1]channelm = 0
```

marketresult	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
0						
atc4classes	.1105562	.0731059	1.51	0.130	-.0327287	.2538411
iudg	.9059952	.4021175	2.25	0.024	.1178593	1.694131
eff	1.05893	.6001935	1.76	0.078	-.1174274	2.235288
ai	1.136674	.533286	2.13	0.033	.0914525	2.181895
otc	.6784261	.5018017	1.35	0.176	-.3050872	1.661939
galform	.2085023	.5398536	0.39	0.699	-.8495913	1.266596
channelm	1.451722	.6527227	2.22	0.026	.1724093	2.731035
_cons	-1.399584	.3973106	-3.52	0.000	-2.178299	-.6208698
1						
atc4classes	.1105562	.0731059	1.51	0.130	-.0327287	.2538411
iudg	.9059952	.4021175	2.25	0.024	.1178593	1.694131
eff	1.05893	.6001935	1.76	0.078	-.1174274	2.235288
ai	1.136674	.533286	2.13	0.033	.0914525	2.181895
otc	.6784261	.5018017	1.35	0.176	-.3050872	1.661939
galform	.2085023	.5398536	0.39	0.699	-.8495913	1.266596
channelm	1.451722	.6527227	2.22	0.026	.1724093	2.731035
_cons	-4.186829	.5616923	-7.45	0.000	-5.287726	-3.085932

```
44 .
45 . **Part b.  No variables constrained to meet the pl assumption.
46 .
47 . gologit2 marketresult atc4classes iudg eff ai otc galform channelm, npl lrforce store(uncon
> strained)

Generalized Ordered Logit Estimates              Number of obs   =        130
                                                 LR chi2(14)     =      43.57
                                                 Prob > chi2     =     0.0001
Log likelihood = -95.830122                      Pseudo R2       =     0.1852
```

marketresult	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
0						
atc4classes	.1180929	.0824572	1.43	0.152	-.0435201	.279706
iudg	1.248351	.4598368	2.71	0.007	.347087	2.149614
eff	2.015261	.8585338	2.35	0.019	.3325653	3.697956
ai	.744295	.5847716	1.27	0.203	-.4018363	1.890426
otc	1.218002	.5973135	2.04	0.041	.047289	2.388715
galform	.0579902	.5735324	0.10	0.919	-1.066113	1.182093
channelm	1.510703	.8745016	1.73	0.084	-.2032886	3.224695
_cons	-1.697624	.4501922	-3.77	0.000	-2.579984	-.8152633
1						
atc4classes	.137355	.1534418	0.90	0.371	-.1633855	.4380954
iudg	.676984	.7775887	0.87	0.384	-.8470619	2.20103
eff	-.3553453	1.158443	-0.31	0.759	-2.625851	1.915161
ai	2.898492	.958841	3.02	0.003	1.019199	4.777786
otc	-14.08112	1132.256	-0.01	0.990	-2233.263	2205.1
galform	1.595117	.9913077	1.61	0.108	-.34781	3.538045
channelm	1.156355	1.028133	1.12	0.261	-.85875	3.171459
_cons	-4.688493	1.110123	-4.22	0.000	-6.864294	-2.512693

```
WARNING! 8 in-sample cases have an outcome with a predicted probability that is
less than 0. See the gologit2 help section on Warning Messages for more information.
```

```
48 .
49 . ** Part c.  Do a global test of the parallel lines assumption
50 .
51 .  lrtest constrained unconstrained

Likelihood-ratio test                                 LR chi2(7)  =     19.38
(Assumption: constrained nested in unconstrained)     Prob > chi2 =    0.0071

52 .
53 . ** Part d.  Use autofit to identify/estimate a partial proportional odds model that fits th
   > e data
54 .
55 . gologit2 marketresult atc4classes iudg eff ai otc galform channelm, autofit lrf

------------------------------------------------------------------------------

Testing parallel lines assumption using the .05 level of significance...

Step  1:  Constraints for parallel lines imposed for otc (P Value = 0.9892)
Step  2:  Constraints for parallel lines imposed for atc4classes (P Value = 0.9156)
Step  3:  Constraints for parallel lines imposed for channelm (P Value = 0.8365)
Step  4:  Constraints for parallel lines imposed for iudg (P Value = 0.4679)
Step  5:  Constraints for parallel lines are not imposed for
          eff (P Value = 0.04353)
          ai (P Value = 0.00171)
          galform (P Value = 0.03923)

Wald test of parallel lines assumption for the final model:

 ( 1)  [0]otc - [1]otc = 0
 ( 2)  [0]atc4classes - [1]atc4classes = 0
 ( 3)  [0]channelm - [1]channelm = 0
 ( 4)  [0]iudg - [1]iudg = 0

           chi2(  4) =    0.61
         Prob > chi2 =    0.9619

An insignificant test statistic indicates that the final model
does not violate the proportional odds/ parallel lines assumption

If you re-estimate this exact same model with gologit2, instead
of autofit you can save time by using the parameter

pl(otc atc4classes channelm iudg)

------------------------------------------------------------------------------

Generalized Ordered Logit Estimates                   Number of obs   =        130
                                                      LR chi2(10)     =      39.59
                                                      Prob > chi2     =     0.0000
Log likelihood = -97.820807                           Pseudo R2       =     0.1683

 ( 1)  [0]otc - [1]otc = 0
 ( 2)  [0]atc4classes - [1]atc4classes = 0
 ( 3)  [0]channelm - [1]channelm = 0
 ( 4)  [0]iudg - [1]iudg = 0

------------------------------------------------------------------------------
marketresult |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
0            |
 atc4classes |    .1139987   .0758807     1.50   0.133    -.0347247     .262722
        iudg |    1.061436   .4230764     2.51   0.012     .2322213    1.890651
         eff |    1.914781   .8464328     2.26   0.024     .2558027    3.573758
          ai |    .5766051   .5623142     1.03   0.305    -.5255105    1.678721
         otc |    .8833021   .5353914     1.65   0.099    -.1660457     1.93265
    galform |    .1045803   .5674455     0.18   0.854    -1.007592    1.216753
    channelm |    1.416309   .7055147     2.01   0.045     .0335252    2.799092
       _cons |   -1.503564   .4142028    -3.63   0.000    -2.315386   -.6917411
-------------+----------------------------------------------------------------
1            |
 atc4classes |    .1139987   .0758807     1.50   0.133    -.0347247     .262722
        iudg |    1.061436   .4230764     2.51   0.012     .2322213    1.890651
         eff |   -.9579654   1.231862    -0.78   0.437    -3.372371     1.45644
```

ai	3.334255	.9097707	3.66	0.000	1.551137	5.117373
otc	.8833021	.5353914	1.65	0.099	-.1660457	1.93265
galform	2.130116	.9919806	2.15	0.032	.1858699	4.074363
channelm	1.416309	.7055147	2.01	0.045	.0335252	2.799092
_cons	-5.385883	.8669804	-6.21	0.000	-7.085133	-3.686632

WARNING! 8 in-sample cases have an outcome with a predicted probability that is less than 0. See the gologit2 help section on Warning Messages for more information.

```
. 
. 
. **Analysis with MODEL 3**
. 
. **Part a.  Replicate ologit's results by using the pl and lrforce parameter
. 
. 
. gologit2 marketresult iudg eff ai otc galform channelm, pl lrforce store(constrained)
```

Generalized Ordered Logit Estimates — Number of obs = 131; LR chi2(6) = 20.89; Prob > chi2 = 0.0019; Log likelihood = -107.82567; Pseudo R2 = 0.0883

(1) [0]iudg - [1]iudg = 0
(2) [0]eff - [1]eff = 0
(3) [0]ai - [1]ai = 0
(4) [0]otc - [1]otc = 0
(5) [0]galform - [1]galform = 0
(6) [0]channelm - [1]channelm = 0

marketresult	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
0						
iudg	.9685758	.3947838	2.45	0.014	.1948139	1.742338
eff	1.229691	.5897281	2.09	0.037	.0738449	2.385536
ai	.8959436	.5144726	1.74	0.082	-.112404	1.904291
otc	.7164931	.4970344	1.44	0.149	-.2576763	1.690663
galform	.2136259	.5285154	0.40	0.686	-.8222452	1.249497
channelm	1.503687	.6573013	2.29	0.022	.2154005	2.791974
_cons	-1.185036	.3663527	-3.23	0.001	-1.903074	-.466998
1						
iudg	.9685758	.3947838	2.45	0.014	.1948139	1.742338
eff	1.229691	.5897281	2.09	0.037	.0738449	2.385536
ai	.8959436	.5144726	1.74	0.082	-.112404	1.904291
otc	.7164931	.4970344	1.44	0.149	-.2576763	1.690663
galform	.2136259	.5285154	0.40	0.686	-.8222452	1.249497
channelm	1.503687	.6573013	2.29	0.022	.2154005	2.791974
_cons	-3.912968	.5272063	-7.42	0.000	-4.946273	-2.879662

```
. 
. **Part b.  No variables constrained to meet the pl assumption.
. 
. gologit2 marketresult iudg eff ai otc galform channelm, npl lrforce store(unconstrained)
```

Generalized Ordered Logit Estimates — Number of obs = 131; LR chi2(12) = 40.48; Prob > chi2 = 0.0001; Log likelihood = -98.03122; Pseudo R2 = 0.1711

marketresult	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
0						
iudg	1.29997	.4442438	2.93	0.003	.4292678	2.170671
eff	2.142832	.8521705	2.51	0.012	.4726087	3.813056
ai	.5053146	.55188	0.92	0.360	-.5763503	1.586979
otc	1.214129	.5869398	2.07	0.039	.0637477	2.36451
galform	.0936596	.5653468	0.17	0.868	-1.0144	1.201719
channelm	1.607108	.8821411	1.82	0.068	-.1218569	3.336073
_cons	-1.449878	.4143522	-3.50	0.000	-2.261993	-.6377622
1						
iudg	.753405	.7493448	1.01	0.315	-.7152838	2.222094
eff	-.2274573	1.146728	-0.20	0.843	-2.475002	2.020088
ai	2.675458	.9336828	2.87	0.004	.8454728	4.505442
otc	-12.81933	707.1177	-0.02	0.986	-1398.745	1373.106
galform	1.544115	.9724042	1.59	0.112	-.361762	3.449992
channelm	1.40569	.9818606	1.43	0.152	-.5187215	3.330101
_cons	-4.385999	1.033294	-4.24	0.000	-6.411217	-2.360781

WARNING! 8 in-sample cases have an outcome with a predicted probability that is less than 0. See the gologit2 help section on Warning Messages for more information.

```
68 .
69 . ** Part c.  Do a global test of the parallel lines assumption
70 .
71 .  lrtest constrained unconstrained
```

Likelihood-ratio test — LR chi2(**6**) = **19.59**
(Assumption: constrained nested in unconstrained) — Prob > chi2 = **0.0033**

```
72 .
73 . ** Part d.  Use autofit to identify/estimate a partial proportional odds model that fits th
   > e data
74 .
75 . gologit2 marketresult iudg eff ai otc galform channelm, autofit lrf
```

Testing parallel lines assumption using the **.05** level of significance...

Step 1: Constraints for parallel lines **imposed for otc** (P Value = **0.9842**)
Step 2: Constraints for parallel lines **imposed for channelm** (P Value = **0.9035**)
Step 3: Constraints for parallel lines **imposed for iudg** (P Value = **0.4625**)
Step 4: Constraints for parallel lines **are not imposed for**
eff (P Value = **0.04458**)
ai (P Value = **0.00114**)
galform (P Value = **0.04603**)

Wald test of parallel lines assumption for the final model:

(1) **[0]otc - [1]otc = 0**
(2) **[0]channelm - [1]channelm = 0**
(3) **[0]iudg - [1]iudg = 0**

chi2(3) = **0.60**
Prob > chi2 = **0.8957**

An insignificant test statistic indicates that the final model
does not violate the proportional odds/ parallel lines assumption

If you re-estimate this exact same model with **gologit2**, instead
of **autofit** you can save time by using the parameter

pl(otc channelm iudg)

Generalized Ordered Logit Estimates

Number of obs	=	**131**
LR chi2(**9**)	=	**36.91**
Prob > chi2	=	**0.0000**
Pseudo R2	=	**0.1560**

Log likelihood = **-99.819643**

(1) **[0]otc - [1]otc = 0**
(2) **[0]channelm - [1]channelm = 0**
(3) **[0]iudg - [1]iudg = 0**

marketresult	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
0						
iudg	**1.134627**	**.4148531**	**2.74**	**0.006**	**.32153**	**1.947724**
eff	**2.05597**	**.8399995**	**2.45**	**0.014**	**.4096011**	**3.702339**
ai	**.3672181**	**.5371045**	**0.68**	**0.494**	**-.6854874**	**1.419924**
otc	**.9181759**	**.5306242**	**1.73**	**0.084**	**-.1218285**	**1.95818**
galform	**.1309634**	**.5602293**	**0.23**	**0.815**	**-.967066**	**1.228993**
channelm	**1.521501**	**.7106543**	**2.14**	**0.032**	**.1286443**	**2.914358**
_cons	**-1.288211**	**.3845711**	**-3.35**	**0.001**	**-2.041956**	**-.5344656**
1						
iudg	**1.134627**	**.4148531**	**2.74**	**0.006**	**.32153**	**1.947724**
eff	**-.7154048**	**1.183755**	**-0.60**	**0.546**	**-3.035522**	**1.604713**
ai	**3.189555**	**.9026104**	**3.53**	**0.000**	**1.420471**	**4.958639**
otc	**.9181759**	**.5306242**	**1.73**	**0.084**	**-.1218285**	**1.95818**
galform	**2.100251**	**.9876099**	**2.13**	**0.033**	**.164571**	**4.035931**
channelm	**1.521501**	**.7106543**	**2.14**	**0.032**	**.1286443**	**2.914358**
_cons	**-5.156405**	**.8565871**	**-6.02**	**0.000**	**-6.835285**	**-3.477525**

WARNING! 8 in-sample cases have an outcome with a predicted probability that is less than 0. See the gologit2 help section on Warning Messages for more information.

```
. 
. *4 Post-regression analysis*
. 
. **Marginal effects with a generalised ordered logit regression**
. 
. 
. quietly gologit2 marketresult iudg eff ai otc galform channelm, autofit lrf
```

WARNING! have an outcome with a predicted probability that is less than 0. See the gologit2 help section on Warning Messages for more information.

```
. 
. mfx2
```

Frequencies for marketresult...

scope of the relevant market	Freq.	Percent	Cum.
0	**68**	**51.91**	**51.91**
1	**53**	**40.46**	**92.37**
2	**10**	**7.63**	**100.00**
Total	**131**	**100.00**	

Computing marginal effects after gologit2 for marketresult == 0...

Marginal effects after gologit2
      y = Pr(marketresult==0) (predict, o(0))
         = .51765239

variable	dy/dx	Std. Err.	z	P>|z|	[	95% C.I.	]	X
iudg*	-.2740532	.09397	-2.92	0.004	-.458236	-.08987		.603053
eff*	-.4221667	.11111	-3.80	0.000	-.639935	-.204399		.091603
ai*	-.0914878	.13265	-0.69	0.490	-.351469	.168493		.167939
otc*	-.2225076	.12	-1.85	0.064	-.457699	.012683		.160305
galform*	-.032724	.13997	-0.23	0.815	-.307051	.241603		.152672
channelm*	-.3381805	.12211	-2.77	0.006	-.577518	-.098843		.076336

(*) dy/dx is for discrete change of dummy variable from 0 to 1

Computing marginal effects after gologit2 for marketresult == 1...

Marginal effects after gologit2
      y = Pr(marketresult==1) (predict, o(1))
         = .45061195

variable	dy/dx	Std. Err.	z	P>|z|	[	95% C.I.	]	X
iudg*	.2414111	.08618	2.80	0.005	.072492	.41033		.603053
eff*	.4391543	.11009	3.99	0.000	.223385	.654923		.091603
ai*	-.2074339	.12368	-1.68	0.094	-.449843	.034975		.167939
otc*	.1838497	.09455	1.94	0.052	-.001458	.369157		.160305
galform*	-.1067183	.13869	-0.77	0.442	-.378536	.165099		.152672
channelm*	.2486598	.0749	3.32	0.001	.101866	.395454		.076336

(*) dy/dx is for discrete change of dummy variable from 0 to 1

Computing marginal effects after gologit2 for marketresult == 2...

Marginal effects after gologit2
      y = Pr(marketresult==2) (predict, o(2))
         = .03173566

variable	dy/dx	Std. Err.	z	P>|z|	[	95% C.I.	]	X
iudg*	.0326421	.01887	1.73	0.084	-.004342	.069626		.603053
eff*	-.0169876	.0225	-0.75	0.450	-.061094	.027119		.091603
ai*	.2989217	.11929	2.51	0.012	.065122	.532721		.167939
otc*	.0386579	.03346	1.16	0.248	-.026918	.104234		.160305
galform*	.1394423	.09817	1.42	0.155	-.052959	.331844		.152672
channelm*	.0895207	.07464	1.20	0.230	-.056774	.235815		.076336

(*) dy/dx is for discrete change of dummy variable from 0 to 1

Preparing final results...

Original results are now active. mfx results are stored as gologit2_mfx.

Model **gologit2_mfx** (*Marginal effects after gologit2*)

marketresult	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
0						
iudg	-.2740532	.0939726	-2.92	0.004	-.4582362	-.0898702
eff	-.4221667	.1111082	-3.80	0.000	-.6399348	-.2043985
ai	-.0914878	.1326459	-0.69	0.490	-.3514689	.1684934
otc	-.2225076	.1199976	-1.85	0.064	-.4576986	.0126835
galform	-.032724	.1399653	-0.23	0.815	-.307051	.2416031
channelm	-.3381805	.1221131	-2.77	0.006	-.5775179	-.0988432
1						
iudg	.2414111	.0861848	2.80	0.005	.072492	.4103303

eff	.4391543	.1100882	3.99	0.000	.2233853	.6549233
ai	-.2074339	.1236802	-1.68	0.094	-.4498427	.0349749
otc	.1838497	.0945465	1.94	0.052	-.001458	.3691574
galform	-.1067183	.1386851	-0.77	0.442	-.3785361	.1650994
channelm	.2486598	.0748961	3.32	0.001	.1018661	.3954535
2						
iudg	.0326421	.0188697	1.73	0.084	-.0043419	.069626
eff	-.0169876	.0225039	-0.75	0.450	-.0610944	.0271191
ai	.2989217	.1192877	2.51	0.012	.0651221	.5327212
otc	.0386579	.0334577	1.16	0.248	-.026918	.1042338
galform	.1394423	.0981659	1.42	0.155	-.0529594	.331844
channelm	.0895207	.0746414	1.20	0.230	-.0567738	.2358152

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130 .
131 .
132 .
133 .
134 .
end of do-file

135 . log close
      name:  <unnamed>
       log:  C:\Users\Marie\Desktop\Stata_2014\2004_2011\Results_2004_2011_NEW.smcl
  log type:  smcl
 closed on:  18 May 2014, 16:37:30
```

Annex 4: Description of the variables

Name	**Description**
$c, c > 1$	Information advantage in favour of the originator product over the generic version
$v(t) = t$	Valuation for the treatment
σ	Proportion of physicians of type 0 who are more receptive to the information advantage
θ	Physicians' price sensitivity
δ	Improvement of the products
γ	Investment in R&D