Implications of future EU policy on the provision of medicines and on actors in the European pharmaceutical sector

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ZUSSAMENFASSUNG

Der europäische Arzneimittelmarkt steht seit vielen Jahren im Fokus der Politik. Sowohl die Finanzierung von Gesundheitssystemen als auch der Zugang zu solchen werden auf nationaler Ebene durch steigende Ausgaben für Arzneimittel gefährdet. Der pharmazeutische Sektor ist häufig Gegenstand nationaler Interventionen zur Kostendämpfung, da dieser in der Regel schneller als das Bruttoinlandsprodukt und der gesamte Gesundheitsmarkt wächst. Nationenübergreifend wächst die Rolle der Europäischen Union, die versucht, die Innovations- und Wettbewerbsfähigkeit der strategisch wichtigen europäischen Pharmaindustrie zu stärken. Ziel dieser Dissertation ist es, die wachsende Rolle der EU im europäischen Arzneimittelmarkt, insbesondere in Hinblick auf Akteure und Mitgliedstaaten zu untersuchen. Dies erfolgt in drei Schritten, die im Folgenden zusammenfassend erläutert werden: (1) ein *Review* der Rollen und Trends der Akteure des europäischen pharmazeutischen Marktes, einschließlich der EU und ihrer Mitgliedsstaaten; (2) Entwicklung von *Zukunftsszenarien* für die europäische pharmazeutische Politik; und (3) eine *Analyse* der Auswirkung dieser Szenarien auf die verschiedenen Akteure im europäischen Arzneimittelmarkt.

Im ersten Teil werden die Akteure und der konzeptionelle Rahmen, in dem sie interagieren, dargestellt. Die nationalen Maßnahmen zur Kostendämpfung resultieren in niedrigeren Gewinnmargen auf Anbieterseite (Pharmaunternehmen, Großhandel und Apotheken). Vergleicht man Indikatoren der Wettbewerbsfähigkeit der *forschenden Pharmaindustrie* (Forschung und Entwicklung, Lohn- und Nebenkosten, Anzahl von neuen innovativen Arzneimitteln) zwischen den USA und Europa, liegen diese in Europa (deutlich) unter denen der amerikanischen Konkurrenten. Pharmazeutische *Großhändler* standen in den 1990er Jahren einem dramatischen Konsolidierungskurs gegenüber. Derzeit versuchen sie ihre Konkurrenzfähigkeit durch eine Erweiterung ihres Dienstleistungsangebots (vertikale Diversifikation, bspw. durch Logistikdienstleistungen für Pharmaunternehmen) zu sichern. Die *Apothekenbranche* ist verglichen mit anderen Industriebereichen eine der am stärksten regulierten Branchen überhaupt. Sie weist zudem eine enorme Heterogenität in der Apothekendichte auf und steht zusätzlich den Herausforderungen neuer Apothekenketten und Online-Apotheken gegenüber.

Verglichen mit der Anbieterseite, ist die Nachfrageseite (Verschreiber, Patienten und Kostenträger) durch eine asymmetrische Informationslage gekennzeichnet. Zwar haben *Verschreiber* (Ärzte) in der Regel mehr pharmazeutisches Wissen als Patienten, dennoch hat sich das Arzt-Patienten-Verhältnis aufgrund neuer Informationstechnologien, die einen schnellen Zugang zu medizinischem Wissen ermöglichen (z.B. Internet), verändert. Innerhalb Europas existieren weiterhin erhebliche Unterschiede hinsichtlich Verschreibungs- und Konsumverhalten von Arzneimitteln, die auf kulturelle Unterschiede und nationale Regelwerke zurückzuführen sind. Für gewöhnlich liegt das Interesse der *Patienten* nicht darin, ein möglichst kostengünstiges Medikamente zu erhalten. Doch durch nationale Maßnahmen wie z.B. Zuzahlungsregelungen wird versucht das Bewusstsein der Patienten dafür zu steigern. Die *Kostenträger* (z.B. Krankenkassen) bieten ihre Leistungen innerhalb eines national stark regulierten Umfelds an und haben bisher selbst keine große Rolle in der Eindämmung von Arzneimittelkosten gespielt, was nicht zuletzt an existierenden Gesundheitssystemstrukturen liegt, in welchen es an Instrumenten zur Einflussnahme auf Preis und Volumen von Arzneimitteln mangelt.

Die regulierenden Instanzen auf dem europäischen Arzneimittelmarkt sind die *europäischen Union (EU)* und ihre Mitgliedsstaaten. Die Arzneimittelpolitik der EU wird überwiegend von Seiten der Industriepolitik beeinflusst. Sie ist bestrebt den Arzneimittelmarkt zu liberalisieren und einen europäischen Binnenmarkt (SEM) zu realisieren. In den vergangenen 40 Jahren zeigte die Arzneimittelpolitik einen beachtlichen Trend in Richtung Europäisierung. Dennoch können die 1995 eingeführten verbindlichen europäischen Zulassungsprozeduren und die Aufsichtsbehörde EMEA als letzte große Errungenschaft bezeichnet werden. Die Europäische Kommission hat sich stattdessen der Umsetzung von Empfehlungen der hochrangigen G-10-Arzneimittelgruppe zugewandt. Sie versucht sich auf die Koordination von Ergebnissen zu konzentrieren, statt auf europäisches Sekundärrecht wie z.B. Richtlinien. Entscheidungen des europäischen Gerichtshofs beziehen sich beispielsweise auf das Recht an geistigem Eigentum, Markenzeichen, Patentschutz, Parallelimporten und Online-Apotheken. Sie beeinflussen wiederum die Gestaltung nationaler Politik in Richtung einer Liberalisierung nationaler Märkte.

Obwohl Marktzulassung, Pharmakovigilanz, Klassifizierung von Arzneimittel sowie deren Distribution immer mehr von der EU mitbestimmt wurden, erhielten die europäischen *Mitgliedsstaaten* mit Hilfe des Artikels 152 des EG-Vertrags Kompetenzen bei Preisbildung

und Vergütungen innerhalb ihrer Gesundheitssysteme. Zudem entwickelten Mitgliedsstaaten innerhalb der letzten 25 Jahre zunehmend gleichartige (von einander kopierte) Maßnahmen, um die steigenden Ausgaben für Arzneimittel zu kontrollieren, die oft kurzfristig wirkten, dann allerdings langfristig ohne Erfolg blieben.

Im zweiten Teil der Arbeit werden Zukunftsszenarien der europäischen Arzneimittelpolitik beschrieben. Dazu wurden Schlüsselbegriffe und Variablen europäischer Arzneimittelpolitik aus Publikationen zusammengestellt. Als nächstes wurde ein Delphi Fragebogen entwickelt, mit welchem 41 europäische Experten bezüglich der erarbeiteten Schlüsselthemen befragt wurden. Die Ergebnisse der Delphi Befragung stellten die Bausteine zur Entwicklung eines konsolidierten *„Experten Szenarios“* dar. Daraufhin folgte eine kontrastierende Gegenüberstellung mit einem eher pessimistischen Szenario *(„Europäisches Krisen Szenario”)* und einem eher „optimistischen“ Szenario *(„Europäisches Szenario“)*:

(1) Das *Experten Szenario*: Im Bereich des europäischen Arzneimittelmarktes, in welchem die europäische Gesetzgebung den potentiell größten Einfluss hat, wird eine weitere Europäisierung vorausgesehen. Marktzulassung, Pharmakovigilanz, Einstufung von Arzneimittel, Großhandelsvertrieb und Werbung zeigen einen graduellen Trend in Richtung europäischer Konvergenz. Regulierung und Implementierung von Preisbildung, Abgabe, Verschreibung und Vergütung von Arzneimitteln verbleiben vornehmlich auf nationaler Ebene. Die von den Experten erwartete Europäisierung der vergleichenden Evaluation von Arzneimittel stellt dahingehend eine Ausnahme dar, da sie innerhalb der einzelnen Gesundheitssystems stattfindet, wo eher eine Dominanz der nationalen Kompetenzen vorausgesehen wird.

(2) Das *Europäische Krisen Szenario*: Der europäische Prozess erfährt einschneidende Rückschläge. Hauptsächliche Ursachen hierfür liegen im stockenden Expansionsprozess, einem vorhandenen Imageproblem, einer andauernden europäischen Verfassungskrise und einer pharmazeutischen Krise, die durch ein von der europäischen Zulassungsprozedur genehmigtes Arzneimittel ausgelöst wird. Dies führt zur Rückbesinnung auf nationale Regulierungen und einer Einfrierung des europäischen Prozesses.

(3) Das *Europäische Szenario*: Durch die erfolgreiche Ratifizierung des europäischen Verfassungsvertrages wächst das Vertrauen der Bürger in das europäische Projekt. Das

finanzielle Gleichgewicht der einzelnen Gesundheitssysteme wird jedoch durch immer mehr grenzüberschreitende Patienten gefährdet. Um dem entgegenzutreten erarbeiten die einzelnen Mitgliedstaaten einen gemeinsamen europäischen Leistungskatalog. Dieser führt zu einer Europäisierung der verschiedenen nationalen Gesundheitssysteme, welche ironischerweise nicht durch die europäische Kommission, sondern durch die Mitgliedstaaten selbst initiiert wurde.

Die im dritten Teil der Arbeit behandelten Auswirkungen der Szenarien auf die unterschiedlichen Akteure stellen sich wie folgt dar: trotz der europäischen Bemühungen die *Pharmaindustrie* wettbewerbsfähiger zu machen, ändert sich in Zukunft eher wenig an der wirtschaftspolitischen Lage der forschenden Pharmaindustrie. In keinem der Szenarien scheinen größere Veränderungen hinsichtlich freierer Preisbildung und Vergütungsentscheidungen (d.h. weniger Möglichkeiten Investitionen zu refinanzieren) wahrscheinlich. Dennoch ermöglicht die Größe des europäischen Marktes mit zunehmend harmonisierten Märkten Synergieeffekte, z.B. Marktzulassung und Marketing betreffend.

Für die *Generika-Industrie* stellt sich die Zukunftsaussicht durchaus positiver dar. Zunehmende nationale Maßnahmen mit dem Ziel den Generika-Gebrauch zu stimulieren, erleichtern der Generika-Industrie den Zugang zu vornehmlich ‚unreifen' generischen Märkten. Dennoch erhöht der sich weiter europäisierende Arzneimittelmarkt den Wettbewerbsdruck über nationale Grenzen hinaus und führt zu einem internationalen Konsolidierungsprozess auch innerhalb der Generika-Industrie. Innerhalb des *Europäischen Krisen Szenarios* könnte dieser Wettbewerbsdruck allerdings langfristig geringer bleiben.

Auch *Biotechnologieunternehmen*, für die das Europäische Zentrale Marktzulassungsverfahren obligatorisch ist, haben großes Interesse an einer Weiterentwicklung des europäischen Marktes. Es wäre für sie finanziell sehr aufwändig, für neue Produkte Marktzulassungsverfahren in allen 27 Mitgliedstaaten einzeln durchlaufen zu müssen (wie im *Europäischen Krisen Szenario* angenommen). Biotechnologieprodukte werden jedoch auch zunehmend eingeschränkten Vergütungsentscheidungen unterworfen, die auf vergleichender Evaluation von Arzneimittel basieren. In Anbetracht ihrer hohen Kosten für Forschung und Entwicklung ist der Unternehmenserfolg dieser Unternehmen von Refinanzierung der Forschungs- und Entwicklungskosten besonders abhängig.

Im *Großhandelssektor* wird sich eine internationale Konsolidierungstendenz – sowohl horizontal als vertikal– weiter fortsetzen. Der nationale Großhandel wird in zunehmendem Maße auch über die Staatsgrenzen hinaus operieren, was durch harmonisierende Arzneimittelmärkte ermöglicht wird. Der Großhandelssektor wird darüber hinaus versuchen, seine Dienstleistungspalette zu erweitern und nach Partnern unter Pharmaunternehmen suchen. Nur unter dem *Europäischen Krisen Szenario* sind sie in der Lage, ihre führenden nationalen Positionen infolge unterschiedlicher nationaler Regelwerke und Warenangebote beizubehalten.

Apotheken werden in Zukunft mit vielen Herausforderungen konfrontiert sein, die zu einer Veränderung des gesamten Sektors führen werden. Sie sind in zunehmendem Maße der europäischen Marktliberalisierung und nationalen Maßnahmen zur Kostendämpfung ausgesetzt. In der Annahme, dass sich das *Europäische Krisen Szenario* nicht verwirklicht, ist es also wahrscheinlich, dass das „goldene Zeitalter" der Apotheken zu einem Ende kommt. Resultate dieser Veränderungen könnten unterschiedliche Eigentümerschaften (z.B. Krankenversicherer, Nicht-Apotheker), neue vertikale Kombinationen, Apothekenketten, Abschaffung von Staatsmonopolen (wo noch präsent) und ein größerer Marktanteil von Online-Apotheken (auch ermöglicht durch eine europäisch harmonisierten Produktpalette) sein.

Die Nachfrageseite des europäischen pharmazeutischen Marktes zeigt noch sehr große Divergenz zwischen den Mitgliedsstaaten. Die *Verschreiber* stehen allerdings überall unter wachsendem Druck, rational zu verschreiben, was ihre Verschreibungsfreiheit in zunehmendem Maße einschränkt. Wenn Mitgliedsstaaten das Kostendämpfungspotenzial des rationalen Verschreibens ausschöpfen, werden sich die Unterschiede im Konsum von Arzneimitteln zwischen Mitgliedsstaaten wahrscheinlich im Laufe der Zeit angleichen. Der beobachtete Vertrauensverlust im Arzt-Patienten Verhältnis wird wahrscheinlich weiterhin anhalten, nicht zuletzt da Informationen aus dem Internet (leider auch von zweifelhaften Quellen) leicht verfügbar bleiben werden. Das *Europäische Szenario* verstärkt dabei die Notwendigkeit, sich auf europäischer Ebene den gemeinsamen Herausforderungen in einen Europäischen Gesundheitsmarkt zu stellen, während unter einem *Europäischen Krisen Szenario* die Notwendigkeit weniger ausgeprägt ist.

Die *Patientengruppen* sollten ihre Organisationen stärken, um die stark ausgeprägten Informationsasymmetrien zu vermindern, und sich auf Europaebene eine leistungsfähige Teilnahme zu sichern. Die zusätzlichen Erwartungen der Nationalregierungen, dass Patienten einen Teil ihrer Behandlungskosten übernehmen, betont die Notwendigkeit, die Entwicklungen hinsichtlich Gerechtigkeit (Fairness) des Zugangs zu überwachen. Im Moment scheint es weiterhin ein Potenzial für grenzüberschreitende Lieferungen von preiswerteren oder in den Heimatstaaten nicht abrechenbaren Arzneimittel zu geben. Patientengruppen können diese Möglichkeiten in der Zukunft stärker berücksichtigen und diese Informationen an ihre Mitglieder weitergeben. Durch die sich dadurch wahrscheinlich anschließenden Rechtsstreite könnten sie so eine bahnbrechende Rolle in der Schaffung eines klaren europäischen Regelwerkes spielen. Das dies, wie im *Europäischen Szenario* angenommen, letztendlich zu einem paneuropäischen Gesundheitssystem führt, ist nicht undenkbar, allerdings spielen dabei noch eine Vielzahl anderer Faktoren eine Rolle.

Sowohl im *Experten Szenario* als auch im *Europäischen Krisen Szenario* ist die Auswirkung auf die *Kostenträger* eher geringfügig, da sie in ihrer Entwicklung eher von Entscheidungen nationaler Art abhängig sind. Dies beinhaltet bereits sichtbare Initiativen, die zu mehr Wettbewerb im Versicherungsmarkt geführt haben. Würde sich dagegen das *Europäische Szenario* durchsetzen, könnten Arzneimittel eine katalysierende Rolle im Hervortreten eines europäischen Gesundheitsmarktes spielen, was wiederum zu einem europäischen Krankenversicherungsmarkt, in dem internationale Versicherungskonzerne Policen für einen europäischen (Basis-) Leistungskatalog anbieten, führen könnte. Diese Entwicklung könnte eine internationale Konsolidierung der Krankenversicherer auslösen.

Obwohl im *Experten Szenario* das (europäische) pharmazeutische Regelwerk insgesamt zunehmend europäisch geprägt wird, behalten die einzelnen *Mitgliedsstaaten* die Entscheidungskompetenz hinsichtlich Preisregulierung und Vergütung. Jedoch werden nationale Gesetzgebungen, die nicht-abrechenbaren Arzneimittel und Arzneimitteldistribution unter verstärkter europäischer Beobachtung stehen. Folglich sollten Mitgliedsstaaten ihre gesetzlichen Rahmen prüfen und sie in Übereinstimmung mit europäischem Recht bringen. Die Erwartung, dass abgesehen von den nicht-abrechenbaren Arzneimitteln auch der Generika-Markt zunehmend liberalisiert wird, sollte Mitgliedsstaaten motivieren ihre Preispolitik zu untersuchen, um so einen wettbewerbsfähigen Generika-Markt zu ermöglichen. Die Erwartung, dass eine vergleichende Evaluation von Arzneimitteln

zunehmend auf Europaebene stattfinden wird, heißt nicht notwendigerweise, dass die nationalen Entscheidungskompetenzen bei der Arzneimittelvergütung vermindert werden. Eine verstärkte Zusammenarbeit der Mitgliedsstaaten bei der europäischen (vergleichenden) Arzneimittelevaluierung könnte zu einer deutlichen Effizienzsteigerung führen. Falls sich das *Europäische Szenario* mit einem paneuropäischen Gesundheitssystem durchsetzt, könnten Mitgliedsstaaten zu einer weiteren Zusammenarbeit in Hinblick auf einen europäischen Basiskatalog gezwungen werden, möglicherweise mit zusätzlichem Raum für nationale Kataloge. Anstatt die Idee eines europäischen Basiskataloges kategorisch abzulehnen, wäre es für die europäischen Mitgliedsstaaten sicherlich vorteilhafter, sich auf diese Entwicklung vorzubereiten.

SUMMARY

The European pharmaceutical sector has been an area of continuing political attention for many years. On a national level, the rising expenditures on drugs are posing a threat to the financing and accessibility of health care. Often faster growing than GDP and the health sector as a whole, the pharmaceutical sector has been the subject of many national cost containment strategies. On a supranational level, the EU has an increasing role. Not only does the EU ensure the satisfactory delivery of public health, it is also concerned how to encourage innovation and competitiveness of the strategically important sector. The main objective of this thesis is to examine the impact of future EU regulation and policy on the various stakeholders in the European pharmaceutical market, focusing on industry and Member States. To achieve this goal, the research has been conducted in three steps: (1) a *review* of the roles, historic context and trends of the actors of the European pharmaceutical market, including the European Union and Member States; (2) development of *future scenarios* for EU pharmaceutical policy; and (3) an *analysis* of the impact of these scenarios on the various stakeholders in the EU pharmaceutical sector.

The first part discusses all actors using a conceptual framework. Stringent cost containment measures result in smaller profit margins for suppliers of pharmaceuticals (pharmaceutical industry, wholesalers and pharmacies). The *innovative pharmaceutical industry* lags behind in competitiveness, when compared to the US on such factors as R&D, labour costs and New Chemical Entities launched. The *wholesalers* saw a dramatic European level consolidation trend in the 1990s and try to cope with the competitive environment through expanding their range of services (e.g. logistics for industry). The *pharmacy sector* is one of the most heavily regulated sectors, showing substantial differences across Europe in pharmacies per million inhabitants and is challenged with pharmacy chains and internet pharmacies

The demand side of the pharmaceutical market (prescribers, patients and payers) is characterised by information asymmetry in comparison with the supply side. Although a *prescriber* (doctor) has more pharmaceutical knowledge than a patient, new technologies such as the internet help patients access detailed medical information and change the doctor-patient relationship. Major differences exist across Europe along cultural and national boundaries in prescribing practice and consumption of pharmaceuticals. Traditionally, *patients* do not have an interest to take the cheaper pharmaceutical, but national policies such as co-payments try to

increase patients' interests. The *payer* (e.g. sickness funds) must design an insurance policy in a heavily government-regulated environment and have thus far not played a major role in the containment of pharmaceutical costs, not in the least because of the existing health care structure in which they may lack the instruments to influence price and volume of pharmaceuticals.

The regulators in the European pharmaceutical markets are the *EU* and the Member States. European pharmaceutical policy has been dominated by EU industrial policy, which seeks to liberalise the market and realise a Single European Market (SEM) for pharmaceuticals. Over the past 40 years, a remarkable Europeanisation trend has been observed. However, the 1995 introduction of the legally binding European authorisation procedures and a governing body (European Medicines Agency, EMEA) can be seen as the last major accomplishments. Instead, the European Commission devotes itself to the recommendations of the G10 medicines group and focuses on the coordination of results rather than secondary legislation such as directives. The European Court of Justice's judgements concerning, for example, intellectual property rights, trademarks, patent protection, parallel trade and internet pharmacies, have affected national policies and liberalised national markets.

Although market authorisation, pharmacovigilance, classification and distribution has seen a trend towards European regulation, *Member States* kept the competence inside their health systems with regard to pricing and reimbursement following Article 152 of the Treaty establishing the European Community (TEC). Over the last 25 years Member States increasingly adopted similar measures to cope with the rising pharmaceutical expenditures, which often showed short term rather than long term effects.

The second part of the thesis describes future scenarios for pharmaceutical policy. To this end, key issues and variables of European pharmaceutical policy were selected from published literature. Next, a Delphi questionnaire was developed in which 41 selected European experts were questioned on these issues. The results of the Delphi questionnaire were used as building stones to fill in the *'Expert Scenario'*, which was then contrasted with a more 'pessimistic' scenario (the *'European crisis scenario'*) and a more 'optimistic' scenario (the *'European Scenario'*):

(1) The *'Expert Scenario'*: In the area of the European pharmaceutical market where Europe has most competence and European law has the largest (potential) influence, a further Europeanisation is foreseen. Authorisation, pharmacovigilance, classification, distribution and advertising show a gradual trend towards European regulation. Pricing, dispensing, prescribing and reimbursement, remain predominantly a national competence and just a slight change towards Europe is expected. However, one exception has been identified: post-licensing evaluation, which takes place 'within' the national health systems as a competence of the Member States, is not expected to remain a solely national matter but shows a trend towards European regulation.

(2) The *'European Crisis Scenario'*. The European process suffers major setbacks, mainly caused by the stalling expansion process, a pervasive image problem, an enduring European constitutional crisis and a pharmaceutical crisis involving pharmaceuticals authorised through a common European procedure. This eventually leads to a return to national regulation and a freeze of the European process.

(3) The *'European Scenario'*. After the successful passing of the European Constitution, the citizens gain trust in the European project. Member States increasingly 'suffer' from border-crossing patients. This threatens the financial balance of their health care systems and action is required: the Member States work out a deal on a common European benefit basket. This leads to a Europeanisation of the various national health systems that ironically is not instigated by the European Commission, but by Member States.

In the third part, the impact of these scenarios on the various actors is analysed. Despite European efforts to make the pharmaceutical industry more competitive, the future may not alter much in the problems facing the *innovative industry*. In each of the scenarios, it does not seem likely that there will be much change with regard to less restrictive pricing and reimbursement decisions, possibly resulting in less opportunities to retrieve investments. Yet the sheer size of the increasingly harmonised European markets enables synergy effects regarding marketing and market launching.

For the *generic industry*, the outlook may be more positive. They will be helped by favourable generic policies (generic substitution, faster market access) and existing 'potential' of immature generic markets. Competitiveness is also likely to increase as a result of increasing

foreign competitive pressure, leading to more (international) consolidation. Under the *European Crisis scenario* competitive pressure may be less.

Highly innovative *'new biotechnology firms' (NBFs),* for which the centralised authorisation is obligatory have a vested interest in the continuous development of a European market. They may lack the means to file 27 different authorisation procedures (which they would have to under the *European Crisis scenario*). However, biotech products are also subjected to restrictive reimbursement decisions, which are increasingly based on cost-effectiveness studies. This makes them especially vulnerable considering their high research and development (R&D) costs.

The European *wholesaling sector* will continue to see an international consolidation trend, both vertically and horizontally. Wholesalers not only purchase and distribute within national boundaries, but increasingly engage in cross-border purchasing and distribution, enabled by converging pharmaceutical markets. The wholesaling sector may cope by expanding their range of services and search for partners among pharmaceutical industry. Only under the *European Crisis Scenario* are they able to retain their leading national position mostly owing to divergent national frameworks and product ranges.

Pharmacies will be faced with many challenges, leading to a completely different operating environment. They are increasingly the subject of European market liberalisation and national cost-containment policies. It seems likely that their 'golden days' will gradually come to an end on the assumption that the *European Crisis Scenario* does not materialise. The result will be different sorts of ownership (e.g. insurer-owned, non pharmacist-owned), new vertical combinations, chaining of pharmacies, abolishment of state monopolies and the emergence of internet pharmacies enabled by increasingly harmonised products on sale in Europe.

The *demand side* of the European pharmaceutical market still shows huge differences between Member States. The *prescribers* will be under growing pressure to prescribe rationally and their freedom to prescribe as they see fit may be increasingly challenged. Consumption pattern differences are likely to converge over time when high consumption countries realise the cost containment potential of rational prescribing. Furthermore, the observed loss of trust in the patient-prescriber relationship is not likely to abate. Information is readily available on the internet and will only increase, unfortunately also from dubious

sources. The *European Scenario* reinforces the necessity to organise at European level to face common challenges, while under a *European Crisis Scenario* the need may be less essential.

The various *patients* groups should bolster their organisations to counter information asymmetry and in order to participate more effectively in European level discussions that may have far reaching consequences for them. The increased expectation by national governments that patients bear an increasing part of the costs stresses the need to monitor developments regarding equity of access. There seems to be, as yet, potential to obtain cheaper and, in the home state, non-reimbursed pharmaceuticals through the cross-border delivery of pharmaceuticals. Patient groups can look into this and signal opportunities to their members. They could play a pioneering role, also through litigation and articulation of these options, and force clarity in these frameworks. Whether this would lead to the emergence of a European health system as assumed in the *European Scenario* depends on many factors, but is not inconceivable.

In the *Expert Scenario* and the *European Crisis Scenario* the impact of these scenarios on the payers is negligible. Payers will develop in ways decided at a national level. Their development is likely to contain visible national trends to bring some form of managed competition in the insurance market. In addition, would the *European Scenario* materialise, pharmaceuticals play a catalysing role in the emergence of a European health market and, possibly later, a European health insurance market in which international insurers offer health insurance policies for a European basic health basket. This could also provoke an international consolidation trend between health insurers.

Although in the *Expert Scenario* the European pharmaceutical framework with regard to e.g. authorisation, classification (although nationally implemented) and wholesaling will turn European, the Member States retain the regulatory overhand on vital decisions in their respective health systems. However, all national legislation that interferes with non-reimbursed medicines is likely to become under intensified European scrutiny. Furthermore, the regulatory framework for the pharmacy and wholesaling sector is expected to be liberalised over the next twenty years. Therefore, Member States should assess these frameworks to bring them more in line with European law. The expectation that apart from the non-reimbursed medicines markets, the generic market will increasingly be liberated should motivate Member States to assess their pricing policies in order to facilitate a

competitive generic market. The expectation that post-licensing evaluation will be increasingly regulated on a European level does not necessarily take away the national competence to make individual Member State decisions. Therefore, it makes sense for Member States to support collaboration in this field as it will help them in carrying out this task more efficiently. If the *European Scenario* materialises and a European health system develops, Member States could be forced into a European collaboration on a basic benefits basket, possibly with additional national catalogues. Instead of categorically refusing the idea, it may be prudent to study it in order to be prepared.

INTRODUCTION

The European pharmaceutical sector has been an area of continuing attention for many years. On a national level, the rising expenditures on drugs are posing a threat to the financing and accessibility of health care. Often faster growing than GDP and the health sector as a whole, the pharmaceutical sector has been the subject of many national cost containment strategies.

Although pharmaceutical policy is primarily considered a national concern (pricing and reimbursement), the European Union (EU) has an increasing role. Not only does the EU ensure the satisfactory delivery of public health, it is also concerned how to encourage innovation and competitiveness. The pharmaceutical sector, a high growth and innovation intensive industry, is a main provider of employment and the main contributor to the European trade balance and thus of high strategic importance. Subsequent reports drafted for the Directorate-General for Enterprise points out that Europe is 'lagging' behind in competitiveness in comparison with the USA (Gambardella et al. 2000; Pammolli et al. 2004). Indicators like Research and Development (R&D), size of the European industry and growth rate, point out that the European Pharmaceutical sector is losing out to their main competitors. Furthermore, current EU policy –mainly resulting from European law– is exerting influence. This includes the Four Freedoms (goods, workers, capital and services), European competition law and the EU Social Chapter. These result in expanding regulations, such as anti-trust laws, and an increasingly harmonised marketing authorisation procedure, but also European Court of Justice (ECJ) rulings that have significant influence on the way Member States organise their health systems.

The EU's ultimate goal of a Single European Market (SEM) has been restricted to attempts to liberalise the market. Member States are unwilling to give up their regulatory authority as in other industrial sectors, because –depending on their specific policy goals– they fear the outcomes for domestic industry (i.e. job loss) and for their respective health care systems (i.e. more reimbursable products and/or higher prices for pharmaceuticals). This fear holds back national support and often emerges in the use of the subsidiarity principle.

The High Level Group on Innovation and Provision of Medicines (G10), constituted in March 2001 by the European Commission, resulted in a series of recommendations regarding the European pharmaceutical sector. This report examined how the EU can achieve the seemingly dichotomous goal of innovation (competitiveness) and provision (accessibility), and provides

a direction for EU policy. The G10 recommendations could be seen as a break from the traditional approach of harmonisation in favour of a more realistic approach of co-ordination of national results instead of the underlying rules themselves. It is hitherto unclear, however, what the implications of the process that was initiated by the G10 recommendations, combined with traditional EU policy would mean for the various stakeholders in the European pharmaceutical sector. This uncertainty hampers national support and threatens to constrain the whole process towards a Single European Market for pharmaceuticals.

This thesis seeks to estimate the impact of the increasing role of EU policy on the Member States in the European pharmaceutical market. What are realistic and feasible scenarios for the future course of pharmaceutical policy and what are the implications for the delicate balance between the social nature of health services and the national competence on the one side, and internal market legislation and the European competence on the other side? What will be the impact on the organisation of the pharmaceutical sector? It will also attempt to answer whether EU policy will result in more competitive industry and better provision. Do national governments have legitimate reason to be concerned about the impact of EU-policy on national policy? Will it imply job-loss, more expensive medicines or restrictions in accessibility through changes to the list of reimbursed pharmaceuticals?

Objectives

The main objective of this thesis is to examine the impact of future EU regulation and policy on the various stakeholders in the European pharmaceutical market, focusing on industry and Member States.

Scope of the thesis

The thesis includes all EU Member States. However, since the EU only recently has been expanding eastwards, emphasis is placed on the original EU15 Member States and its historical context. Furthermore, all actors in the pharmaceutical market are included, but emphasis lies on supply side actors and Member States. The period of 1960-2025 is used as a timeframe for the thesis.

In achieving this goal, the research was conducted in three steps:

1. A **literature review** of the roles, historic context, characteristics and visible trends of the actors of the European pharmaceutical market, including the European Union and Member States.
2. Development of **future scenarios** for EU/Member State pharmaceutical policy.
3. An **analysis** of the impact of these scenarios on the various stakeholders in the EU pharmaceutical sector.

Research strategy, methods used and structure of thesis

This thesis has a qualitative approach. A literature review provides the basis and background for the scenarios. A scenario is a compilation of trends into differing images of the future. Scenarios are a tool for considering how interacting sets of trends might lead to a range of conditions in the future (Garrett 1999). It provides more opportunities to move into uncharted territory. The building of scenarios consists of the following fundamental components, as described in the World Health Organization (WHO) commissioned 'Health futures. *A handbook for health professionals*' (Garret 1999):

- Clarifying issues
- Acquiring information
- Analysing the system
- Describing past and present
- Imagining future trends
- Framing the scenarios
- Filling in the scenarios
- Evaluating the scenarios
- Applying the results.

Using such a structured approach means that important issues are not easily overlooked and it contributes to the validity and reliability of the research. Applied to the three-step approach, the following plan was developed and implemented:

Part I: Literature review

Tasks:

- *Clarify issues*: Which issues need to be addressed and which issues will be given priority? This step was necessary to ensure that nothing was overseen and that the scope of the research was made clear. This is step is described in the here present Introduction Chapter.
- *Acquire information*: A literature research was carried out. Therefore, search criteria were drafted which were used in the following strategy:
    - Searching 'grey' sources of information. Searching internet using conventional search engines
    - Searching online databases. Searching PubMed, EconLit, IBSS, Decomate II and Medline
    - Searching European Commission Documents and ECJ rulings
    - Manual search of relevant journals such as Pharmacoeconomics, Health Economics, Journal of Health Economics, Health Planning and Management and Health Policy
    - Systematically tracing back relevant references
- *Analyse the system*: In this step, information is analysed in order to develop understanding of the structure or system under consideration (Garret 1999). Activities were: determining the structure of the pharmaceutical market, identifying which input variables are important and identifying the actors and their strategies used. What are their goals, activities, resources, limitations, behaviour, interests, mechanisms, schemes and relations? The result of this step is a conceptual framework of the pharmaceutical market, presented in Chapter 1.
- *Describing past and present*: A review was written on the current state of the European pharmaceutical market, including actors (Chapter 2), European Union and European pharmaceutical policy (Chapter 3) and national pharmaceutical policy (Chapter 4). This provided the starting point from which the scenarios commence.

Part II: Building scenarios

Tasks:

- *Imagining future trends and events*: A list of uncertainties and trends for the future was formed through systematic scanning of environmental factors such as social

dynamics, economy, technology and politics. Then, projections of current trends in key variables were made. The products resulting from this component include any projections carried out on trends in key variables plus the generated list of possible future trends and events. Applied to the European Pharmaceutical market, trends and or events were the full adoption of G10 recommendations, or more national autonomy, which made the key variable ranging from *EU regulation* to *national regulation.*

- *Framing scenarios*: In this stadium, assumptions were made. These assumptions are often expressed as conditional phrases like: 'if G10 recommendations are adopted' or 'if SEM for medicines could be achieved, the future would look like …'. In this thesis a base scenario (based on current trends) was constructed, which was then contrasted with a more pessimistic and a more optimistic scenario. Another possibility could have been to generate two axes of uncertainty (a spectrum), using the information found at the previous step (imagining future trends and events). These axes could then have been used to build a matrix (two axes crossing), which would result in four different quadrants and four different scenarios. However, in order to conduct a feasible research and analysis, this approach was discarded. The Delphi-technique was used as a tool in making assumptions. The Delphi technique is a procedure aimed at obtaining a reliable consensus of opinion from a group of experts through a series of questionnaires interspersed with controlled feedback (Garret 1999). In these questionnaires, experts were asked on key issues what they expect to be the situation in, for example, 2010, 2015 and 2025. After two rounds, a consensus in the trends became visible on the various issues, providing the building stones for a most likely (base) scenario. The chosen methodology is discussed in detail in Chapter 5 and the results in Section 6.1.

- *Filling in scenarios:* After a decision was made about the frame, the scenarios were filled in. The frame was set by the assumptions and key variables about the future. The construction process involved finishing these assumptions and elaborating what would happen if the assumed conditions actually existed in future. This includes outcomes on key issues (the ones addressed in *clarify issues,* step 1), as well as narrative descriptions (Section 6.2) for which literature review was consulted (Chapters 3 and 4).

Part III: Analysis

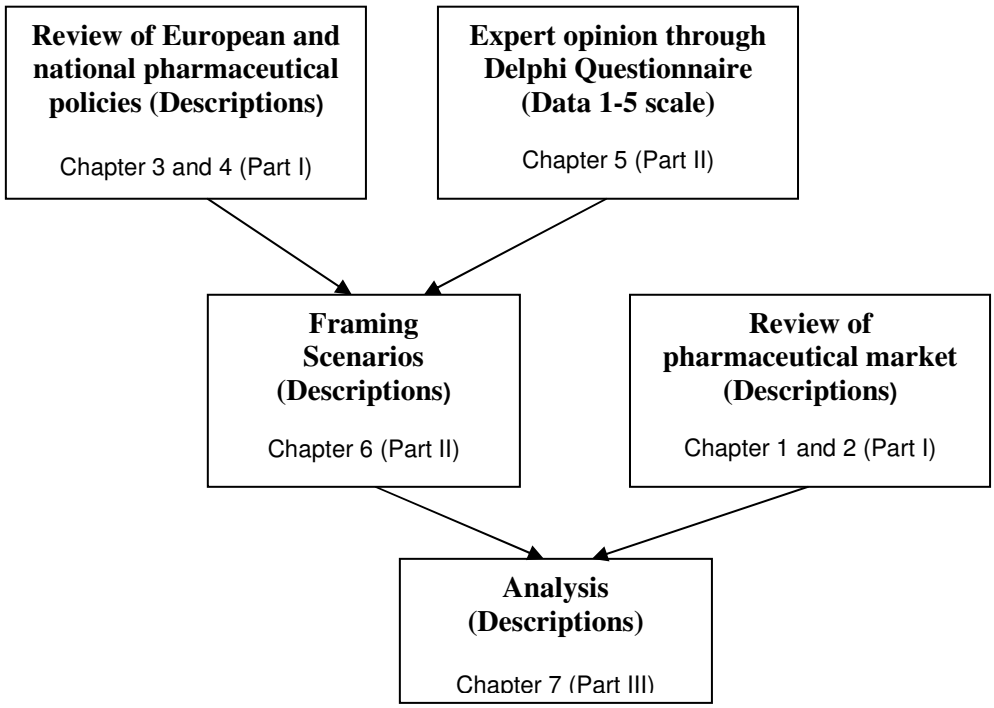
Tasks:

- *Evaluation of scenarios:* Through systematic analysis and interpretation of the scenarios and using the information from step 1, the impact of the scenarios on the various stakeholders was made on key issues (Chapter 7). What are the threats and opportunities the imagined scenarios would bring?
- *Application of scenarios*: After the scenarios have been created and their implications identified, the results of work can finally be applied (Garret 1999). In the application stage, the results of the evaluation were interpreted after which advice and recommendations were given in the form of a discussion.

Methodological background

It is important at this point to note that the analysis in Part III bases itself on certain hypothetic assumptions. These assumptions, which were made while framing the scenarios, are based on interpretations of the data provided by international experts in the form of the results of the European pharmaceutical policy questionnaire. To boost the validity of these scenarios, experts have been selected according to several criteria and questioned on several pharmaceutical policy-relevant topics (see Part II of this thesis). The interpretations of this data (also see figure 1 for a schematic depiction) , which came in the form of numbers on a five point Likert scale, was done using the knowledge and findings of an extensive review of European and national policies (Chapters 3 and 4 of Part I of this thesis). In Part III these scenarios are interpreted in the light of the findings from Chapter 1 and 2 (Part I of this thesis). To increase the transparency of the analysis, references are used there where the analysis bases itself on previous research and on references from Part I of this thesis.

Figure 1 Schematic structure of thesis



PART I: REVIEW

1 CONCEPTUAL MODEL OF THE EUROPEAN PHARMACEUTICAL MARKET

The pharmaceutical market is a very complex market, which is subjected to competing policy goals and interests and numerous public interventions. The many actors with conflicting views make the market far from transparent. Not only are there different policy goals and perspectives *between* the various actors in the market, but also *within* actors; the national governments for example, have to serve health goals as well as industrial policy goals. Because there are so many actors, it is useful to try to fit them in a conceptual model, which will then provide an insight into who has influence and what kind of influence they wield. Therefore, this Chapter will discuss a simple model of the European pharmaceutical market, which will be used as a basis for analysis further on in this thesis. The bases of this model are the pharmaceutical value chain and the medical care triad. Next, the other actors are filled in, together with their policy perspectives and functions. The model makes clear that the European pharmaceutical market actually consists of three markets on different levels (Schut 1993). The vertical chain producer-wholesaler-pharmacist forms the supply side of the pharmaceutical market: the pharmaceutical value chain. On the demand-side we find the consumers (patients), prescribers (physician) and payers. On all levels, European and national regulation exert influence.

The value chain consists of several links (see figure 2). The first link is formed of the *manufacturers*, the pharmaceutical industry and importers of pharmaceuticals. These manufacturers and importers form the first market on which they deliver their product to *wholesalers*. There are roughly three different kinds of manufacturers: Manufacturers of innovative pharmaceuticals, manufacturers of generics and the 'new biotechnology firms' (NBFs).

Innovative, branded pharmaceuticals are mostly on-patent, which allows the company to sell the product without competition and 'win back' the investment costs it made in Research and Development (R&D). As soon as the pharmaceutical gets off-patent, other producers can enter the market and produce the drug, set their own price and try to compete for market share. These off-patent drugs, known as generics, are close to perfect substitutes and can be expected to compete on price (Mrazek and Frank 2004). The innovative industry has higher R&D costs, but can expect a high return of investment if they have one of their new drugs

licensed and reimbursed. Another important aspect of this market is that it is highly international. Many of the innovative companies involved are multinationals who deliver their products not along domestic boundaries, but internationally. The generic industry is more likely to operate within national borders.

On the second market, wholesalers distribute the pharmaceuticals to *pharmacies*. There are two types of wholesalers: full-line wholesalers and short-line wholesalers. The former provide the full range of drugs and either operate on a national or regional level, the latter provide a specialised limited range, often at competitive prices. Not all European countries allow short-line wholesalers (e.g. France and Italy) because there is a perceived public interest (Taylor et al. 2004a). In contradiction with globally operating manufacturers, most wholesalers traditionally conduct their business within the domestic market, although there is an observed trend of consolidation, fuelled by the pursuit of economies of scale. Different kinds of pharmacies in number and form exist within the EU. Most important European variants are the community pharmacy and the hospital pharmacists. A significant development is the emergence of mail-order and online pharmacies. Because of public health priorities and its key position in controlling pharmaceutical expenditures, pharmaceutical distribution is subject to strong national regulation. It is important to notice that the lines between manufacturers, wholesalers and community pharmacies become blurred in cases where there is vertical integration between them (Taylor et al. 2004a). This 'second' market has many international characteristics, though not to the same degree as the first market.

On the third market, the drug gets dispensed to the *consumer*. The physician (doctor, GP) *prescribes* the drug, with the prescription the consumer collects the pharmaceutical and receives reimbursement by the *payer*. Characteristic of this third market is the strong information asymmetry between the demand side (consumer, payer and prescriber) and the supply side (manufacturer, wholesaler, and pharmacist). Furthermore, because individual costs can mount significantly, it is an insurance market, in which the payer has to facilitate access to drugs for the most vulnerable groups in the population. The insurance system takes away the stimulus for the consumer to opt for an inexpensive pharmaceutical, which increases chances for moral hazard substantially. The prescriber, in essence, is chiefly occupied with prescribing the pharmaceutical he deems appropriate, regardless of price. This last market is dominantly national, and is subject to various strict national regulatory frameworks. The medical care triad depicts the health insurance market in a fundamental way to illustrate that

payers mediate between the provider and patients. The triangle makes up the bottom part of the model and forms the demand side of the pharmaceutical market.

It is important to note that the pharmaceutical market as a whole is not just these three markets. These markets in turn consist of highly fragmented smaller markets for specific therapeutic classes of pharmaceuticals, in which certain manufacturers are strongly represented, often domineering for the time they are protected by patents. The pharmaceutical market therefore knows many monopolistic and oligopolistic market structures. Another relevant classification in this respect is the existence of drug markets for 'prescription only medicines' (POM), which mainly consists of (largely) publicly reimbursed innovative and generic drugs, and 'over the counter' (OTC) drugs, also referred to as 'non-prescription pharmaceuticals'. These classifications and definitions are not exhaustive, as will become clear later on in this thesis.

National governments and the European Commission are not a direct part of the pharmaceutical value chain, but both have had an increasingly important role within the European pharmaceutical market. National governments and the European Commission exert influence on all levels being the most important policy maker and legislative power. One cannot conceive either a national government or the European Union as one single actor. Both have different departments and institutions, which represent different stakes and views. All these departments and institutions try to influence the actors, according to their respective policy goals. Generally, there are two main competing pharmaceutical policy interests: health policy and industrial policy (see Table 1). But also within health policy, two possibly conflicting perspectives can be distinguished: the health care perspective and the public health perspective.

In the national situation, health policy comes from the Member State's equivalent of the Ministry of Health. Industrial policy is advocated through the Ministry of Trade or Industry. On a supranational level, the Directorate General for Health and Consumer Protection mainly advocates a public health policy objective, not so much a healthcare perspective. Industrial policy is the domain of the Directorate General for Enterprise and Industry.

Table 1 Competing policy objectives regarding pharmaceuticals

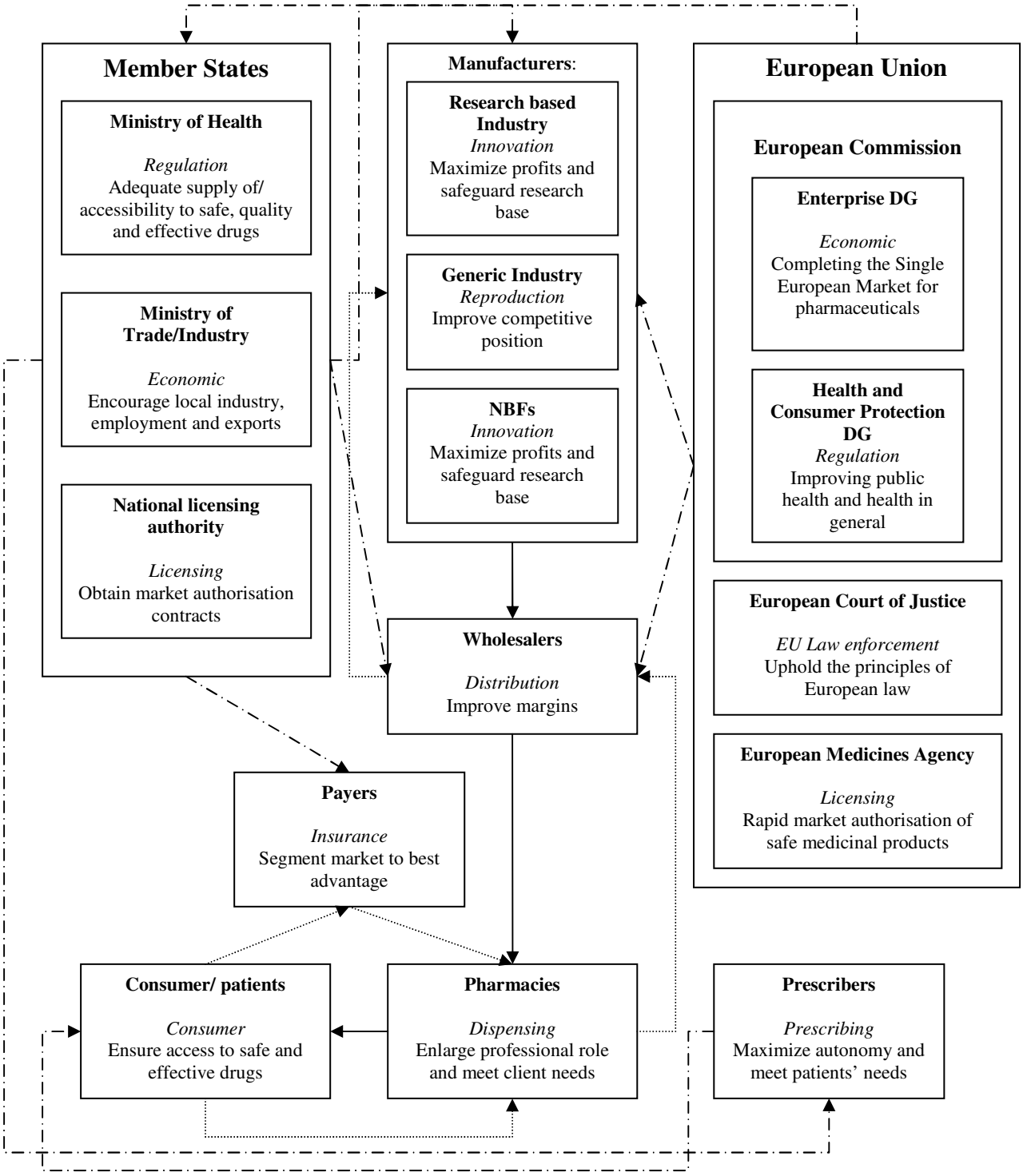
Health policy		Industrial policy
Health care perspective	**Public health perspective**	
Cost containment and improving efficiency in health services and care	Safe medicines	Promoting local research and development capacity
Cost effective medication	High-quality preparations	Intellectual property rights protection
Regulating doctor and consumer behaviour vis-à-vis medicines	Efficacious treatments	Supporting local scientific community
Generic promotion and or substitution	Innovative cures	Generating and protecting employment
Improving prescribing	Patient access to medicines	Promoting small an medium enterprise policies
Ensuring access to medicines		Contributing to positive trade balance
		Sustaining the university research base

Source: Permanand and Altenstetter (2004)

Responsible for the admission of pharmaceuticals to the European markets are the European Medicines Agency (EMEA) and the respective national licensing authorities. If a pharmaceutical company seeks market admission to more then one Member State, it can achieve that through the centralised procedure (EMEA) or through the decentralised procedure (via a national licensing authority). When a pharmaceutical company seeks a market admission to only one Member State, it can achieve that through a solely national procedure (through a national licensing authority). The EMEA is regulated by the DG Enterprise and Industry. As a last actor wielding considerable influence the European Court of Justice (ECJ) has to be mentioned. The ECJ's task is to uphold the principles of European law, including the free movement of goods and free competition. When a conflict arises between national practice and European law, ECJ rulings can have important implications for national policies.

In the following Chapters of Part I, the actors of the pharmaceutical market will be elaborated upon. Chapter 2 describes the supply and demand sides of the European pharmaceutical market whereas Chapters 3 and 4 discuss the roles of the European Union and the Member States respectively.

Figure 2 Stakeholders in the European pharmaceutical market: functions and policy objectives.



Based on: Nyfer (1997) and Permanand and Altenstetter (2004)

2 THE EUROPEAN PHARMACEUTICAL MARKET: A DESCRIPTION

In this Chapter, the European pharmaceutical market is described, according to the model laid out in Chapter 1. This Chapter mainly seeks to describe the characteristics and trends of the actors, such as size and market behaviour. The regulation that applies to these stakeholders is written down in Chapters three and four.

The European pharmaceutical market (see table 2) is one of the largest in the world, hovering roughly between 26 to 30 per cent of the world share in the last decade. Moreover, the pharmaceutical sector provides a significant contribution (over €22 billion in 2001 and over €30 billion in 2004[1]) to the EU trade balance and is the fifth largest industrial sector in the EU, amounting to 2.8 per cent of the total manufacturing production for EU15 and to 2.71 per cent for EU25 (Eurostat in: Pamolli et al. 2004). In comparison to the North American market –roughly the same size at the beginning of the 1990s– the European market is not growing at the same rate as the US market. None the less, European pharmaceutical trade involves many people on different levels, and is –almost without exception– of considerable economic importance to all European Member States.

Table 2 Size of the market for pharmaceuticals 1989-2003

	1989	1990	1995	1998	1999	2000	2001	2002	2003
Total (USD Billion)									
World	155.3	165.8	280.3	300.6	332.6	357.3	389.4	424.8	491.7
Regional Share (%)									
North America	34.0	32.4	31.2	39.2	41.5	44.0	47.2	48.4	46.7
Europe	31.0	26.5	29.6	28.4	26.3	23.7	24.0	25.0	27.5
Africa/ Australia/ Asia	30.0	35.1	32.4	25.1	25.9	25.8	22.9	21.7	21.4
Latin America	5.0	5.9	6.8	7.4	6.2	6.5	6.0	4.9	4.5

Source: IMS International in: Pammolli et al. (2004)

In Europe (2003), the largest markets are Germany (€24 631 million), France (€22 583 million), Italy (€15 592 million), Spain (€10 794 million) and the UK (€10 386 million). They are the largest global markets after the US (1st) and Japan (2nd; IMS International in: Pammolli et al. 2004). In the next Sections, the supply side and demand side of the European market will be discussed.

[1] According to Eurostat on DG Enterprise site, accessed 01/08/2007.

2.1 Supply side

The supply side of the pharmaceutical market, i.e. the pharmaceutical value chain, is often referred to as the 'golden chain' because of the high profits that can be achieved by manufacturers, wholesalers and pharmacists. However, the operating environment has changed over the last decade. Governments have been putting more emphasis on cost-containment, in this way putting more pressure on profit margins of all suppliers of pharmaceuticals. Another important development is new technologies, most notably the emergence of 'life sciences' and the increasing role of the internet. The former enabled new processes of drug discovery and development for the pharmaceutical industry, while the latter is challenging the distribution and pharmacy sector with online pharmacies.

2.1.1 European pharmaceutical industry

Historically, big pharmaceutical industries and major innovations were the domain of German and Swiss companies, a position that was increasingly challenged after World War II by US and UK based firms. In the years following World War II, the pharmaceutical industry experienced a boom, spurred by new research opportunities created by advances in the field of synthetic drugs. This ushered in the first 'golden age' of the pharmaceutical industry. Through this boom, the industry acquired the status of a growing and innovation intensive industry of considerable significance to a country's economy and public health. This newly acquired status deteriorated somewhat over the Thalidomid disaster in the 1960s (also see Chapter 3), the waning innovation dynamics in the 1970s and the increasing criticism of the burden pharmaceutical costs constitute in the health budget (Feick 2000).

The Thalidomid disaster raised awareness of safety of medicines and pharmacovigilance, and consequently, national regulatory mechanisms were put in place throughout Europe during the 1960s –in analogy with the European Community involvements (see Chapter 3). In the early years, these regulatory systems mainly safeguarded the quality and accessibility of pharmaceutical provision (public health perspective), but as early as the 1980s, containing pharmaceutical expenditures (health care perspective) became more and more a policy objective in European States. This made the pharmaceutical industry's operating environment even more difficult. More stringent pricing and reimbursement regimes were the result, which affected the structure of demand in all the major markets.

Furthermore, new technological developments in the field of life sciences caused not only a complete overhaul of the processes of drug discovery and development, but also higher Research and Development (R&D) costs. This development, in combination with increasing pressure through cost containment policies, resulted in more globally operating companies seeking 'economies of scale', often through mergers, joint ventures and acquisitions, doing larger, more costly and internationally based clinical trials. Developments in legislation and in courts' interpretation of issues concerning intellectual property rights, as well as the increasing openness of domestic markets to foreign competition, have influenced patterns of industrial competition and the evolution of industry structure (Gambardella et al. 2000). These developments imply an increase in the resources needed to develop new drugs, and led to a reorientation towards core competencies like R&D and innovation, but also marketing and distribution.

Industry structure

The European pharmaceutical industry exists of two types of pharmaceutical producers: the manufacturers of patented (innovative) drugs and the manufacturers of generics. The innovative industry consists of globally operating, multinational companies, which cover between 40 to 60% of most national markets in the advanced countries (Gambardella et al. 2000). These companies typically are represented in many countries on different continents. Although they have a good share of activities and sales in their own domestic market, they set divisions and activities in other countries and regions as well, particularly in Europe and the US. These are highly R&D intensive companies with large R&D and marketing divisions whose products can earn back their investment through a patent, which allows them to have a temporary monopoly.

The generic industry typically exists of smaller national companies, operating almost exclusively in their domestic market. They are specialised in the sales of off-patent (generic), non R&D-intensive pharmaceuticals and conduct mainly manufacturing and commercialisation activities, and do not invest in R&D (Gambardella et al. 2000). Off-patent drugs are free for other companies to produce and consequently, there is more price competition in their segment, and prices can be expected to be lower than in-patent drugs.

In the last twenty years a new sort of companies has emerged among these national companies. New research-intensive companies sprung off from the opportunities opened up by life sciences– the so called New Biotechnology Firms (NBFs). These companies are

specialised in biotechnology and their activities range from the discovery and development of new drug compounds to the development of new drug screening or research tools and technologies in fields like genomics and bioinformatics. Crucial for these NBFs is competing for finance, in order to develop products, after which they must compete for attention from the large multinationals that are the market incumbents and have the necessary sales channel. The multinationals are keen to put the biotech products in their portfolios through 'biopartnering'(EuropaBio 2005).

The European pharmaceutical industry is a high growth manufacturing stronghold in many Member States, with the largest pharmaceutical production in France, which generated a production value of €34 495 million in 2001, Germany with €23 251 million and the UK with €17 224 million (see table 3).

Table 3 Production value, pharmaceuticals (NACE 24.4) constant million € 1995-2001

Country	1995	1996	1997	1998	1999	2000	2001
France		23554	26002	27891	29868	33065	34495
Germany					20870	22158	23251
United Kingdom		10265	13111	12979	14375	15782	17224
Italy	11954	14696	13732	14703	15843	15342	15674
Spain	6190	6411	6117	6165	6427	6872	7528
Belgium	4143	4033	4051	4041	5059	5672	6655
Netherlands	3283	4069	4601	4853	5217	5494	5489
Denmark	2216	2505	2866	3081	3467	3318	3910
Ireland	1732	1699	2086	2337	3618	3932	3898
Austria	1468		1657	1919	1777	2432	1781
Finland	665	652	732	688	704	755	826
Portugal	921	811	915	740	813	790	729
Slovak Republic	175	197	196	164	144	143	158
Czech Republic	314	295	311	248	244	313	329
US	67394	70671	74917	82214	95446	117460	114039

Source: Eurostat and OECD in: Pammolli et al. (2004)

The leading pharmaceutical corporations in the European market are also among the leading corporations in the world (see Tables 4 and 5). Largest competitor in the European pharmaceutical market is –after the heavily contested 2004 takeover of German-French combination Aventis by the French company Sanofi-Synthelabo– the new combination Sanofi-Aventis with a market share of 8.5% (2005), followed by American owned company Pfizer with 7.2% and Swiss owned company Novartis with 5.9%. The largest ten companies in Europe have a market share of 47.2%.

Table 4 Leading pharmaceutical corporations (turn-over) worldwide in 2005

Rank	Corporation	Millions (€)	Market Share (%)
1	Pfizer	39341	8.4
2	GlaxoSmithKline	28820	6.2
3	Sanofi-Aventis	24553	5.3
4	Novartis	23212	5.0
5	Johnson & Johnson	21100	4.5
6	AstraZeneca	19917	4.3
7	Merck&Co	19516	4.2
8	Roche	16276	3.5
9	Abbot	13073	2.8
10	Wyeth	12230	2.6
	Subtotal	218039	46.8
	Total worldwide	466016	100.0

Source: IMS in: GIRP (2005)

Table 5 Leading pharmaceutical corporations (turn-over) in Europe in 2005

Rank	Corporation	Millions (€)	Market Share (%)
1.	Sanofi-Aventis	10051	8.5
2.	Pfizer	8564	7.2
3.	Novartis	7041	5.9
4.	GlaxoSmithKline	7024	5.9
5.	AstraZeneca	5671	4.8
6.	Roche	4559	3.8
7.	Merck&Co	3835	3.2
8.	Johnson & Johnson	3723	3.1
9.	Wyeth	3016	2.5
10.	Lilly	2642	2.3
	Subtotal	56124	47.2
	Total Europe	118794	100.0

Source: IMS in: GIRP (2005)

According to the European Federation of pharmaceutical industries and associations (EFPIA, 2004), the *research* based pharmaceutical industry accounts for about 3.5% of the total EU manufacturing value added and for 15% of the whole EU business R&D expenditures. Furthermore the European research based industry currently employs 588 000 people, of which 100 500 in R&D units. R&D investment in 2002 was at €20 200 million (up from €7 900 million in 1990) and the trade surplus amounted to €36 000 million in 2002. According to the European Generic Medicines Association (EGA 2003), their members, the European generic industry, employ over 100 000 people.

The European biotechnology industry comprises of 1976[2] companies, mainly in Germany (525), the UK (455) and France (225), employing 94 000 people of whom 35 000 in R&D (EuropaBio 2005).

The Pammolli reports on competitiveness of the European pharmaceutical sector

In 2000 a report was drafted for the Directorate-General for Enterprise (Gambardella et al. 2000), addressing the European industry's competitive position in a global environment– the so called Pammolli Report on 'Global Competitiveness in Pharmaceuticals, a European Perspective'. It states that the European pharmaceutical industry has been a stronghold of the European industry, providing by far the largest contribution to the European trade balance in high-technology, R&D intensive sectors. It is a main provider of employment and –last but not least– they produce pharmaceuticals, which are of major importance in achieving public health policy goals in all countries. It is for these reasons, that the European pharmaceutical industry is regarded as an area of strategic importance for welfare in the European Union. But now this sector has been showing cracks in its fundaments. The report shows that the European pharmaceutical sector is losing out vis-à-vis the United States, and provides four conclusions:

1. The European pharmaceutical sector is more labour intensive than US or the Japanese industry. The US and Japanese industries rely more than Europe on non-labour inputs such as capital or most likely R&D. Consequently, there is less pronounced specialisation in R&D activities, and there is a larger presence of non R&D intensive firms. Furthermore, in the 1990s European pharmaceutical industry has grown less than US industry, which stems mostly from an acceleration of the US industry growth, which originates to a good extent from the growth of its non labour inputs (including R&D). Also, these developments cannot be seen apart from the effects of national regulatory regimes (pricing policy etc.).
2. Globally operating multinationals compete largely on new innovative products -new chemical entities (NCEs)- based on substantial R&D investments. In the 1990s, US companies have gained clear and growing leadership in terms of sales generated by the NCEs. The portfolio of products held by the European multinationals tends to be older than that of US firms. The US firms enjoy a comparative advantage in selling their

[2] In the EuropaBio (2005) study, only 15 European countries are surveyed, namely the EU 15 excluding Luxembourg and Greece, complemented with Norway and Switzerland. Therefore, this number does not take into account the new accession countries.

new drugs. The US market grew much faster after being roughly the same size as the European Market in the beginning of the 1990s. And, although these multinationals operate internationally, the bulk of the sales still lie in their own markets.

3. The relative position of the US as a locus of innovation in pharmaceuticals has increased during the 1990s, compared to Europe. Europe has been unable to give rise to a full fledged industry of innovation specialist companies and technology suppliers like in the US, and European companies rely increasingly on sources of research capabilities and innovation in the US. The US biotechnology industry gave rise to a large number of new jobs and to new world-class drug companies (e.g. Amgen, Chiron, Genzyme and others), and several new drug tool companies and produced a stream of revenues in the form of royalties from licenses or R&D contracts and collaborations.
4. The national European markets –some more than others– are not competitive enough. The report illustrates this by showing data of prices and market share after patent expiration. In a competitive market, a price drop –and entry of cheaper generics– is a typical consequence of patent expiration, but in many European markets, there is no substantial change. This nurtures inefficient behaviour and lack of competitiveness.

The report was one of the main reasons for the instalment of the G10 medicines Group and the European Commission adapted the vision displayed in the report on headlines. Strengthening the competitiveness of European pharmaceutical industry has been an important EU industrial policy objective since (see Chapter 3).

In a 2004 update by Pammolli et al. (2004), it becomes clear that the European Industry is still behind in R&D and factors other than labour for its activity (i.e. on capital and R&D). Even if the European pharmaceutical industry has experienced a substantial reduction of the share of labour cost on the value of production in 2000 and 2001, the European industry is still labour intensive compared to the US. This adds to the fact that the share of added value over production is still lower in Europe than Japan and the US. The US firms still lead in terms of innovative activities, sales and geographical diffusion of NCEs launched on the market place. Although European corporations have increased their market shares and the share of total sales from newly introduced products, they still are behind the US firms.

These patterns were, as far as the biotechnology sector is concerned, confirmed in the 2005 report 'Biotechnology in Europe: 2005 Comparative Study' drafted for the European

Association for Bioindustries (EuropaBio). The report states that the European biotechnology sector does not 'compete' with the US sector in terms of any measurable value, e.g. number of employees, R&D, revenues and venture capital raised, with the notable exception of company numbers – European entrepreneurs establish companies at a 50% higher rate than the US. The report identifies 'the financing gap' as the main obstacle for a competitive European biotechnology industry, which results in a high amount of collapsing companies after 3 to 5 years.

2.1.2 Wholesalers

The wholesaling sector has undergone the same trends as visible in the pharmaceutical industry sector. Due to competitive pressures, stringent national market regulation and decreasing profit margins –approximately 27% since the beginning of the 1990s– a dramatic consolidation trend in the last decade occurred, which slowed down somewhat between 2000 and 2004 (Clement et al. 2005). This trend leaves winners with a new strategic orientation and large market shares. In the early 1990s, there were approximately 600 nationally operating full-line wholesalers in the EU15 countries, compared to 151 as of 2004 (Clement et al. 2005). In between countries there are considerable differences in the number of wholesalers. Of the 600 national full-line wholesalers in 1992, 70 % were based in Italy and Spain (Taylor et al. 2004a), but the consolidation trend is visible throughout Europe. For example, from 1992 to 2002, the number of wholesalers in Italy went down from 259 to 149, from 25 to 16 in Germany, from 19 to 11 in France, from 20 to 14 in the UK, from 41 to 27 in Belgium and from 7 to 4 in the Netherlands. In the new accession country Poland, the number went down from 600 to 250 in the same period (Long 2002). The effect of this development is that in many European markets the three largest wholesalers have huge market shares varying from roughly 40% to 95%. In 2002, the actual percentages varied from about 36% (Spain), 43% (Italy), 62% (Germany), 75% (France), to as high as 85% in the UK (Long 2002). This, effectively, makes the wholesale market in many of the Member States an oligopoly. As of 2004, the EU22[3] had 673 regional and national full-line wholesalers (cf. EU15 holds 418 of this total), which operate a network of 1458 warehouses (Clement et al. 2005). The European countries that still have a relatively high number of wholesalers, mainly the new Member States, will probably continue to see the consolidation trend, but in other Member States' markets, further concentration might be met with anti-trust law.

[3] EU25, minus Cyprus, Malta and Slovakia

Another strategic response to cope with increasing competitive pressures is –where legally permitted– vertical integration, which creates new combinations, blurring the traditional division between actors in the pharmaceutical value chain. Many combinations are observed: Integration between wholesalers and pharmaceutical industry, with the pharmaceutical company owning the wholesaler (e.g. Italian manufacturer Angelini and Italian wholesaler Adivar) or a wholesaler having generic production facilities, wholesalers owning their own pharmacies (e.g. OPG in the Netherlands), or pharmacy associations owning their own wholesaler (e.g. Sanacorp in Germany). An example of far reaching vertical integration is retail chain Boots[4], which includes manufacturing, purchasing, distribution and retailing capabilities. Another interesting example is the planned takeover of mail-order pharmacy DocMorris by wholesaler Celesio, which hopes to facilitate the establishment of the first pharmacy chain in the German Market (IHT 2007). Celesio expects that –in Germany forbidden– pharmacy chains will have to become reality through the liberalising effect of EU law. This also applies to other countries such as Austria and Spain.

As the process of horizontal and vertical integration in some countries reaches its limits, wholesaling companies also seek a competitive advantage by increasing the range of services beyond their traditional logistics function. These additional services create an added value for manufacturers as well as distribution partners (retail pharmacies) and may be provided for free. For example, full-line wholesalers increasingly offer 'pre-wholesaling' services, e.g. warehousing, storage, distribution and financial administration, to pharmaceutical manufacturers (Clement et al. 2005).

While these companies started of as national wholesalers, many of them are also penetrating other countries' markets through takeovers and mergers. According to the European Association of Pharmaceutical Full-line Wholesalers (GIRP 2003), leading 'pan-European' companies (presence in more than 10 European countries) are: Alliance UniChem, Celesio and Phoenix. Other major more domestically oriented European companies are Anzag, Noweda and Sanacorp (Germany), Cerp Rouen (France), OPG (Netherlands), United Drug (Ireland) and Galenica (Greece). In 2004, the three leading European wholesaling companies held a market share of 43.4% in the EU15 and a 46.5% market share in the EU22 (Clement et al. 2005). Although major wholesalers purchase pharmaceuticals on a European level, the wholesaler-pharmacy relationship is conducted within national boundaries. Even in the case

[4]In July 2006, Boots Group and wholesaler Alliance UniChem merged to create 'Alliance Boots'.

of multinational wholesalers, the pharmacies are supplied by the locally based subsidiary. This is not the least because of differing controls on product price mark-ups (Taylor et al. 2004a), but also because of different packaging, leaflets and language requirements resulting from previously non-harmonised national legislation.

Parallel trading

Parallel trading is now well established among the main European wholesalers. Initially, wholesalers were reluctant to participate in this trade, mainly of fear of profit loss and a bad relationship with their suppliers, the pharmaceutical industry, which is actively opposing parallel imports. The wholesalers find themselves backed by the parallel trade supporting European Commission. However, an ECJ ruling challenged the Commission's ability to force the pharmaceutical industry to provide unlimited volumes of medicines to parallel importing wholesalers when it overturned a 1996 European Commission fine worth 3 Million ECU on the Bayer Group for limiting the supply of Adalat[5] (also see 3.4.2).

The benefits of parallel trade in terms of benefits for patients and health budgets are heavily debated. Three major studies have dominated the public debate on parallel trade. The first study, commissioned by the (parallel trade promoting) European Association of Euro-Pharmaceutical Companies (EAEPC)[6] and carried out by the York Health Economics Consortium, found evidence that parallel imports have indirect competitive effects by forcing down the price of the domestic counterparts resulting in direct and indirect savings from the parallel trade (West and Mahon 2003). A second study by the London School of Economics (LSE), partially funded by pharmaceutical company Johnson and Johnson, draws an opposing conclusion. It concludes that benefits to patients and health care systems are negligible and that the main beneficiaries are the parallel-importers (Kanavos et al. 2004). In an attempt to settle these opposing views, the EAEPC commissioned the University of Southern Denmark to review the theoretical arguments and empirical evidence concerning parallel imports. The report concludes that parallel distribution generates considerable savings, both direct saving to patients and health payers, up €441.5 million in 2004 in Denmark, Germany, Sweden and the United Kingdom. Furthermore, the level of savings and differences between countries depend to a large extent on the way countries have incentives in place to stimulate the use of the

[5] Case T-41/96 R. Bayer AG vs. The Commission of the European Communities (Adalat).

[6] The European Association of Euro-Pharmaceutical Companies (EAEPC) is the professional and representative body of pharmaceutical parallel trade in Europe aimed at promoting free movement of medicinal products. Its membership mounts to over 70 firms from 16 countries in the European Economic Area (EEA).

imported product instead of the local product, but also on the way measures are in place (e.g. claw backs) so that savings are passed on to the health system and eventually the patient. To overcome the losses through parallel trade, manufacturers have developed defensive strategies, such as controlled supply of raw materials (licences), restrictive distribution agreements, product differentiation, multiple small batches and supply restrictions, i.e. limiting sales to win market share (Enemark et al. 2006)

2.1.3 Pharmacies

The pharmacist traditionally has been responsible for the safe dispensing and in some cases manufacturing of medicines. His role herein is strictly separated from the doctors' responsibility of prescribing the pharmaceutical. However, some considerable exceptions exist –and existed. For example, until the late 1940s, many English GPs dispensed the medicines they prescribed. Also in Austria GPs in more remote rural areas were involved in dispensing. In the Netherlands, there still are about 490 Pharmacy-owning GPs, so called *'Apotheekhoudende Huisartsen'* (RIVM 2004a), down from about 636 in 2000 (RIVM 2004b), which is about 6% of the total GP number in the Netherlands, mainly established in rural areas.

There are about 117 000 community pharmacies across the EU15 Member States (see table 6). Between countries there are significant differences in pharmacies per million. Greece for example has more than seven times as many pharmacies per million inhabitants as the Netherlands, and the Netherlands' neighbouring country Belgium has about 5 times as many pharmacies per million inhabitants. In general, southern European countries have more pharmacies than northern European countries. In most countries community pharmacies outnumber hospital pharmacies by between 12:1 (Belgium, Denmark) and 25:1 (Spain and Germany). In the Netherlands this ratio is about 6:1 (Taylor et al. 2004a).

Table 6 Number of pharmacies in the EU15

	Number of Pharmacies	Pharmacies/ million inhabitants (ranking)
Austria	1 086	134.1 (14)
Belgium	5 273	517.0 (2)
Denmark	1 556	293.6 (6)
Finland	795	152.9 (13)
France	22 689	383.9 (4)
Germany	21 590	263.0 (9)
Greece	8 348	787.5 (1)
Ireland	1 186	320.5 (5)
Italy	16 382	287.4 (7)
Luxembourg	79	197.5 (12)
Netherlands	1 600	101.3 (15)
Portugal	2 778	277.8 (8)
Spain	19 439	493.4 (3)
Sweden	1 889	212.2 (10)
United Kingdom	12 311	207.6 (11)
EU15 total	117 000	

Source: Paterson et al. (2003)

Significant developments are chaining of pharmacies and the emergence of mail order pharmacies. Where permitted, pharmacies are chaining in varying degrees in Belgium, Ireland, Italy, the Netherlands and the UK. The development of mail order and online pharmacies was highly controversial and is opposed by many pharmacists, who think that medicines should be dispensed under supervision in a conventional pharmacy and fear decreasing revenues. However, after initial warnings concerning buying medicines on the internet (PGEU 1999), the Pharmaceutical Group of the European Union (PGEU), which represents community pharmacists in 29 European countries including most EU Member States, does not disapprove of online pharmacies and wants to collaborate on the development of the use of internet and the emergence of e-health and e-enhanced pharmacy applications (PGEU 2001). Key in their view is that all national and European regulation should apply equally to online services. That internet pharmacies often work under illegal conditions is illustrated by a Finnish study (Mäkinen et al. 2005), which distinguished three groups of online pharmacies operating in Europe: legally practising online pharmacies, (often illegal) life-style pharmacies and (totally illegal) rogue sites.

Examples of the first, legally practicing internet pharmacies are new online pharmacies such as the Dutch company DocMorris[7], the largest online pharmacy on the German market, and Pharmacy2u[8], the largest mail order and online pharmacy in the UK. Some of these emerging online pharmacies are in various constructions affiliated with pharmaceutical industry, insurance companies or wholesalers. Furthermore, there are two dimensions that need to be taken into account when discussing internet pharmacies. First, internet pharmacies that work on a national level, i.e. within national boundaries, and second, pharmacies that engage in cross-border activity. In the latter case, a whole new complicating dimension applies as national pharmaceutical markets are still divergent with regard to regulatory framework and, as a result, what is on sale, i.e. which pharmaceutical received authorisation, how is it classified, labelling leaflets et cetera. This could pose serious difficulties especially with regard to the free movement rules. For example, if pharmaceuticals that have not obtained market authorisation for the importing Member State can be ordered online, this could result in an obvious circumvention of the existing obligation to obtain market authorisation. Manufacturers would then be able to obtain authorisation in the Member State with the least stringent legislation and release products into circulation in Member States in which they have no authorisation (De Clippele 2004). Furthermore, the existence of barely legal and non-regulated internet pharmacies which supply drugs from unknown sources, possibly counterfeits, implies grave safety risks for the consumer. It may be superfluous to say that this is an unacceptable situation for Member States.

The situation arisen around DocMorris may shed some light on this complex of problems. DocMorris was established in the Netherlands in 2000 in order to circumvent restrictive regulations concerning mail-order pharmacies and prescription drug prices in Germany. In its short history, DocMorris has had to overcome many problems posed by German legislation and the fierce resistance –often through litigation– of the German Pharmacists Association (ABDA). Using a favourable ECJ ruling on 11 December 2003[9] based on the free movement rules and an already planned change of German legislation in 2003 concerning mail-order services to its advantage, DocMorris managed to force a breakthrough in the German pharmaceutical retail market. The ECJ made clear that border crossing mail-order pharmacy services are compatible with EU law, but also took the view that a national prohibition on mail order sales of prescription drugs can be justified. This did not affect DocMorris as the

[7] See: www.docmorris.com
[8] See: www.Pharmacy2U.co.uk
[9] Case C-322/01, 'Deutscher Apothekerverband eV versus DocMorris NV

German prohibition was (as planned) abolished in 2004 by the amended German Pharmaceutical Act. Nevertheless, DocMorris continues to see strong opposition in the German market, especially in their attempts to establish a pharmacy chain which is problematic under current (German) ownership regulation.

2.2 Demand side of the pharmaceutical market

The demand side of the pharmaceutical market is characterised by information asymmetry in comparison with the supply side. But also on the demand side alone, i.e. within the medical care triad, there are differences in this respect. In general, a doctor has more pharmaceutical knowledge than a patient. However, new technologies such as the internet help patients access detailed medical information, which changes the doctor-patient relationship. The payer must design an insurance policy often in heavily government-regulated environment and deal with agency problems such as moral hazard.

2.2.1 Prescribers

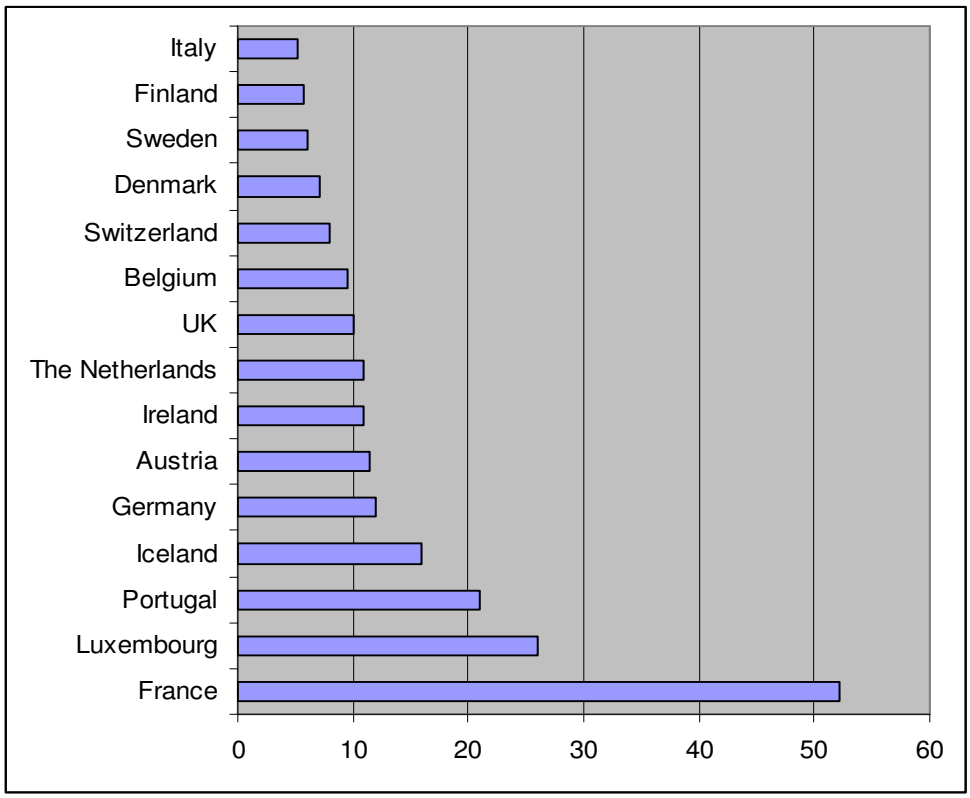
The prescriber, a specialist or general practitioner (GP) is responsible for prescribing the right pharmaceutical, a pivotal role in the provision of pharmaceutical products. Historically, the doctor's main priority and interest is providing the best possible advice or treatment and, if necessary, the prescription of a medicine of good quality, irrespective of costs. However, developments in pharmaceutical expenditures raised awareness among both policy makers and professionals that a rational prescribing behaviour could be a way to contain costs. Therefore, many national governments now have measures or collaborating initiatives aimed at influencing prescribing behaviour (see Chapter 4).

The knowledge doctors possess on the subject of pharmaceutical products might exceed that of patients, but still there is huge information asymmetry compared to the supply side of the pharmaceutical market. This makes them a possibly profitable marketing target. Direct visits from pharmaceutical company detailers support this. Marketing activities by pharmaceutical companies mainly targeted at professionals to 'plug' their latest products have been

circumscribed in recent years by many national governments and –since 1992– by an EU Directive[10].

Furthermore, there are significant differences in numbers of prescriptions –and thus consumption– between countries. This is the result of different cultural attitudes but also of different health care systems (see figure 3). According to Yuen (1999), France leads with an average of 52.2 prescriptions dispensed per capita in comparison to about 5 prescriptions dispensed per capita in Italy and to roughly 6 prescriptions dispensed per capita in Finland and Sweden.

Figure 3 Prescriptions dispensed per capita in some European countries (1996)



Source: Yuen (1999)

Table 7 shows that there is divergence among the percentage of diagnoses made followed by a prescription, reflecting a different prescribing behaviour. In more recent but rougher data for 2003, Italy's percentage of diagnosis with prescription was well over 90%, for Belgium and Spain it was more than 80%, for France more than 75%, for England and Germany around 70% and for the Netherlands slightly over 60% (IMS Health in: Nefarma 2004).

[10] Directive 92/28/EEC on the advertising of medicinal products for human use, now integrated in 2001/83/EC on the community code relating to medicinal products for human use.

Table 7 Percentage of diagnoses with prescription in some European countries in 1996

	% Diagnosis with prescription
Netherlands	56
Germany	70
UK	74
Spain	79
France	83
Belgium	87

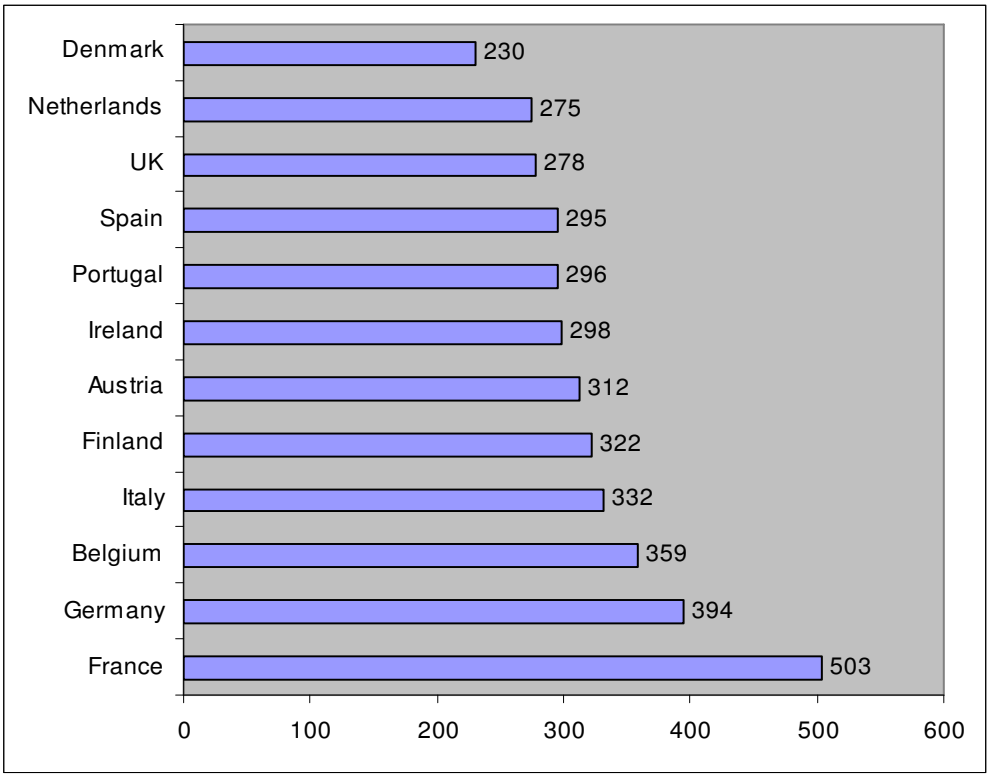
Source: IMS Health in: PriceWaterhouseCoopers (1999)

2.2.2 Patients

Due to developments on the patient's side, the doctor-patient relationship is changing. Patients become more involved in choice of treatment and have access to an abundance of medical information, not in the least through the internet. Another important development is the observed loss of trust in the medical profession. There is an emerging trend across Europe to put more information and more power in the hands of the patients with regard to accessing and using medicines (Bradley et al. 2004). This is illustrated by the fact that in many countries more pharmaceuticals have been made available over-the-counter and have to be paid for out of pocket, which increases the patient's responsibility.

Furthermore, the consumption of pharmaceuticals varies widely across cultural and national boundaries. Different attitudes toward pharmaceuticals exist, displaying their respective cultural values. These result in differences up to twice the total drug consumption per capita within the EU (see figure 4). For example, in France, total drug consumption via pharmacies is €503 per capita, whereas in Denmark this number is 'only' €230. Belgium consumes pharmaceuticals worth €359, which is 1.3 times more than neighbouring country the Netherlands (€275). It is important to note that these differences are jointly determined by a price and volume component. Hence, both factors are subjected to country specific national frameworks, e.g. price and volume regulation, and do not have to be determined by cultural factors alone. Another determinant worth mentioning in this context is the level of generic penetration, which varies significantly between Member States and could have a mitigating effect on pharmaceutical expenditures. Nevertheless, it does give an indication about the magnitude of the differences in consumption patterns in the EU.

Figure 4 Pharmaceutical expenditure (€) per capita through pharmacy in 2004



Source: SFK (2006)

As a further illustration, many studies exist that look into the differences in pharmaceutical consumption patterns between countries, nationalities and ethnic groups. Data from the European Surveillance of Antimicrobial Consumption (ESAC), for example, show that for 2002, France ranks first among the EU25 Member States with an outpatient antibiotic use of 32.22 Defined Daily Dose (DDD) per 1000 inhabitants, compared to 9.83 DDD per 1000 inhabitants for lowest consuming the Netherlands. The study shows that differences in selection pressure account for geographic variation of resistance; countries in southern and Eastern Europe generally consume more antibiotics than countries in northern Europe and higher rates of antibiotic resistance exist in those high-consuming countries (Goossens et al. 2005). However, some interesting regional differences occurred. Belgium for example, ranks sixth among the EU25 with an outpatient antibiotic use of 24.54 DDD per 1000 inhabitants, i.e. 2½ times that of the neighbouring Netherlands. This springs from different attitudes toward disease. Deschepper et al. (2002) found that Belgians worry more about the disease and were more used to leaving the consultation room with a prescription. The Belgians rated their upper respiratory tract diseases often as bronchitis and Dutch mostly as a cold or the flu and never as bronchitis. Moreover, the Belgians more often consulted their doctor when ill

and mostly were prescribed antibiotics, whereas in the Netherlands the patients mostly nursed one's own illness, sometimes in combination with OTC medicines and home remedies.

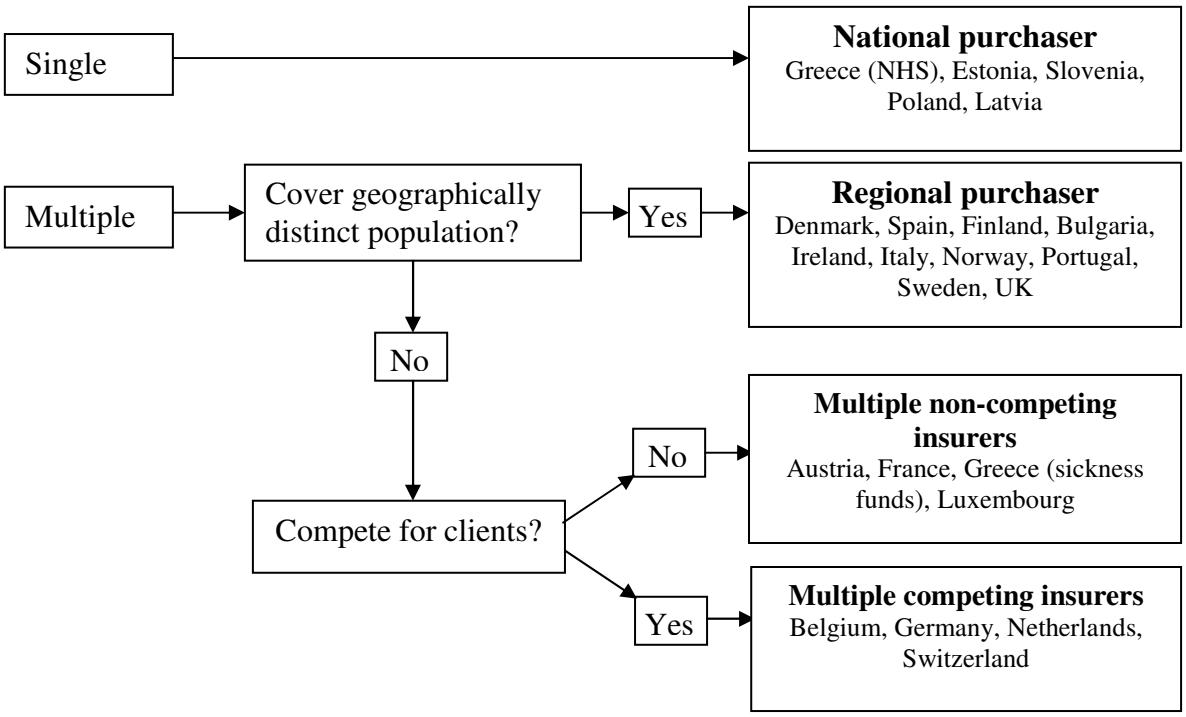
Traditionally, patients do not have a direct interest to take a cheaper pharmaceutical and moral hazard belongs to the problems that the payers are faced with. However, national policies try to increase patients' responsibility and interest through measures such as co-payments and reference pricing (see Chapter 4).

On the macro level, patient groups in general are not as well-organised compared to other actors. They lack financial means and their influence on pharmaceutical policy making is limited. Patient organisations are often fragmented along disease areas with (possibly) conflicting interests and as a consequence do not speak with one voice. This could make patient organisations vulnerable to marketing efforts (through funding of patient groups) of the pharmaceutical industry. This is a newer development in Europe but well-established in the United States. Although this may seem a strange alliance, it is a logical partnership between two actors with a shared interest: access to the newest treatments (which benefits patients) for which positive reimbursement decisions (which benefit pharmaceutical industry) are prerequisite. However, pharmaceutical industry and patients' organisations are unequal partners (in terms of funds and information), which can have serious consequences when grants and joint projects with pharmaceutical companies distort and misrepresent their own agenda's (Herxheimer 2003).

2.2.3 Payers

Because individual costs for pharmaceuticals can mount significantly, it is an insurance market, in which the payer has to facilitate access to drugs for the most vulnerable groups in the population. The payer has many faces in the European pharmaceutical market (see figure 5): it can be a sickness fund, an integrated part of a NHS or a private insurer; it may operate on various levels (national, regional); it can operate in a single payer or multiple payer system; it may have to compete with other payers; it can have public or private features; it can reimburse the patient or the provider.

Figure 5 Market structures for payer/purchaser organisations and European examples



Source: Adapted from Kutzin (2001) and Busse et al. (2007)

During the 1970s and 1980s, the payer/purchaser mainly functioned as a financial intermediary providing or reimbursing the necessary services for the population. In the 1980s, increasing cost pressures led countries to implement cost containment policies that aimed to integrate some form of market mechanisms into their systems. During the 1990s, payer/purchasers received more planning and management authority (Busse et al. 2007). In the UK, for example, which operates a tax-based NHS, the separation of the purchaser and provider ('purchaser/provider split') aimed to create an internal market where providers compete for contracts with the payers. These various experiments with active purchasing and selective contracting in which the payer seeks the best offer in terms of value for money and quality for its clients (patients), mainly focussed on establishing competition between health services providers rather than providers of pharmaceuticals.

Payers thus far have not played a major role in the containment of costs for pharmaceuticals, not in the least because of the existing health care structure in which they may not have an interest (e.g. in a strictly financial intermediary function) or simply lack the instruments to exert influence on pharmaceutical costs. In other words, the payers are faced with so called agency problems. Payers cannot get relevant parties to do what efficiency requires.

Consequently, people with more generous insurance spend more on medical care than people with less generous insurance (moral hazard) and providers paid on a fee-for service basis may provide more care due to supplier induced demand than they would if they were not paid per task (Cutler and Zeckhauser 2000). This can, depending on health care system, directly apply to pharmaceutical provision.

Since spring 2004, health insurers in the Netherlands have gained some influence on price of generics through participating in yearly negotiations (the so called 'covenant') together with the Ministry of Health, pharmacists and producers of generics. Aim of this covenant is to diminish the discounts for pharmacists in favour of the consumers. In 2004 this resulted in a 40% reduction of generics on the market and a pledge by the manufacturers to price new generic medicines 40% below the price level of the corresponding original brand name medicine (SFK 2007). On the longer term, plans exist to further enhance the insurer's role, in order to create a 'countervailing power' on the demand side of the pharmaceutical market. After building up the necessary pharmaceutical expertise to counter the information asymmetry, insurers will receive more freedom to purchase pharmaceuticals for their insureds, making them responsible for medicine prices (through negotiation) instead of the government

Another initiative is seen in Germany, where since 2007 sickness funds may conclude discount contracts (so called 'Rabattverträge') with pharmaceutical companies for individual drugs. Under this system, pharmacies are legally obligated to substitute a prescribed drug for a generic drug if the patient's sickness fund has such a discount contract. The legally required substitution of drugs has been criticised in some studies as it may compromise prescribing quality and patient safety (Pruszydlo et al. 2008; Quinzler et al 2008).

3 THE EUROPEAN UNION

Pharmaceutical policy is a very complicated interplay of various actors, which includes national governments, industry, wholesalers, pharmacists, doctors, payers and patients (see Chapter 1). Often these stakeholders have conflicting interests that can vary from country to country. This makes it hard for national governments to achieve their respective policy goals. Although pharmaceutical policy for a large part is determined at a national level, there is nevertheless a considerable amount of EU legislation exerting influence on the Member States' policies, mainly through the use of regulations, directives and decisions[11].
As will become clear in this Chapter, the EU has had an expanding role in this area since its first involvement in the 1960s, with the legal duty to advocate the principles of European Law, including the free movements of goods and free competition, visible in the Community attempt to liberalise the market for pharmaceuticals. The European Commission's struggle to harmonise national policies changed in recent years into a more realistic approach of co-ordination, because countries were not willing to give up their regulatory authority. They fear the outcomes for domestic industry (e.g. jobs) and for their respective health care systems (e.g. higher prices for pharmaceuticals), depending on the Member State's predominant policy objective.

The European Union cannot be seen as a single actor with only one policy goal but consists of various actors and various policies (industrial, social, health), advocated by the various Directorate Generals (DGs), each having a distinct influence on pharmaceutical policy. Since these influences and their origins may seem opaque from outside, this Chapter takes a closer look at the EU and aims to make visible the different influences these policies and actors have (had) on pharmaceutical provision. The first Section discusses the EU policy making process and its main actors. The Sections two, three and four will describe EU policy along three main areas, i.e. industrial policy, EU social policy and EU health policy respectively. In the Sections five and six, two important EU actors, the European Medicines Agency (EMEA) and the European Court of Justice (ECJ) will be examined.

[11] Regulations are binding in their entirety and directly applicable in all Member States; Directives bind the Member States as to the results to be achieved, but have to be transposed into the national legal framework and thus leave a margin for manoeuvre as to the form and means of implementation; Decisions are fully binding on those to whom they are addressed.

3.1 European Union policy process and actors

The EU consists of three pillars. The European Community, which has its origins in the European Economic Community (EEC), form the first pillar. The second pillar consists of Common Foreign and Security Policy. The third pillar consists, after amendments introduced by the Amsterdam and Nice treaties, of Police and Judicial Co-operation in Criminal Matters. Hence, the latter two play a more intergovernmental role and consequently, the Commission and the European Parliament play less of a role. The focus in this thesis is on the first pillar where most EU policies originate. The activities and responsibilities of the EU are set out in the various European treaties (e.g. The Treaty of Rome, The Single European Act, The Treaty of Maastricht).

Governance and political leadership is provided by the *European Council* (basically a special highest-level meeting of Council of the European Union described below) which consists of the Member States' heads of state/government assisted by their Foreign Ministers and the President of the European Commission. The Council has a rotating presidency, with every Member State taking the helm of the EU for a period of six months. During the presidency, the country's representatives chair meetings of the European Council and the Council of Ministers. The Council usually has quarterly European summits.

The *European Commission ('Commission')* is the EU's executive body and is responsible for initiating legislation and the daily management of the EU. Whereas the Council mainly reflects national interests, the Commission is intended to solely act in the common European interest. Its main functions are (1) to propose legislation to Parliament and the Council; (2) to manage and implement EU policies and the budget; (3) to enforce European law (with the Court of Justice); and (4) to represent the European Union on the international stage, for example by negotiating agreements between the EU and other countries. The Commission is currently composed of 27 commissioners for different areas of policy, one from each Member State. The President and the commissioners are nominated by the Council and have to be confirmed by the European Parliament.

The *European Parliament (EP)* reflects the interest of the European people and consists of 785 Members, who are elected every five years by EU citizens. The EP forms one half of the EU's legislature. Its main functions are (1) passing European laws (jointly with the Council),

(2) democratic supervision over the EU institutions, including the Commission; and (3) the EP shares with the Council budgetary authority over the e EU budget.

The other half of the EU legislature is provided by the *Council of the European Union ('Council')*, formerly known as the Council of Ministers. The Council is a platform where national ministers for specific areas of policy meet, reflecting the interest of the Member State they represent. The Council meets in different formations (e.g. pharmaceutical policy relevant areas are 'Social Policy', 'Health and Consumer Affairs' and 'Competitiveness'). The Council's main responsibilities are (1) to pass European laws jointly with the European Parliament; (2) co-ordinate the broad economic policies of the Member States; (3) to conclude international agreements with non-EU countries and organisations; (4) to approve the EU's budget, jointly with the EP; (5) to develop the EU's foreign and security policy; and (6) to co-ordinate co-operation between the national courts and police forces in criminal matters.

The *European Court of Justice (ECJ)* and the Court of First Instance form the judicial branch of the EU. The former will be examined and analysed in more detail in Section 3.5.

3.2 European Union industrial policy

The observation that the European Union leans toward industrial policy rather than health policy has its origins in the factual competences the European Economic Community (EEC), the predecessor of the EU, has had since its inception in 1957 through the Treaty of Rome. Main aim of the EEC was to bring about economic integration between the founding nations Belgium, France, Germany, Italy, Luxembourg and the Netherlands. The EEC sought to lay the foundations of 'an ever closer union among the peoples of Europe' with 'the constant improvement of the living and working conditions of their peoples' and to 'ensure the economic and social progress of their countries by common action to eliminate the barriers which divide Europe'. Central in its aims was the need for steady expansion, balanced trade and fair competition through the establishment of a customs union with a common external tariff; common policies for agriculture, transport and trade ('common commercial policy'); and enlargement of the EEC to the rest of Europe. Pharmaceutical policy, as a result, leans towards an industrial policy perspective, which is also illustrated by the fact that most legislation regarding Pharmaceuticals emanates from the long established DG Enterprise-

Pharmaceuticals Unit, not from DG SANCO. European pharmaceutical policy is therefore mainly aimed at the establishment of a common market for pharmaceuticals with common (rapid) authorisation procedures.

3.2.1. European Union pharmaceutical policy – a history 1960-2000

European involvement in the European pharmaceutical market dates back to the early 1960s, when the Thalidomide Disaster took place. Thalidomide, developed by German firm Grünental, was sold as a sleeping aid and to pregnant women as a remedy to combat morning sickness. Prescription-free Thalidomide, also known under various brand names, among them Contergan in Germany and Softenon in e.g. Belgium, Finland and Spain, proved to be a bestseller in 1961/62 with 20 million tablets per month sold. It did not take long until some horrible side effects became apparent: it caused birth defects. An estimated 8000 malformed children were born in Europe (Scherer 2000), from which an estimated 4000 in Germany alone. The Thalidomide disaster, one of the biggest drug tragedies of recent history, raised awareness that to safeguard public health, no medicinal product must ever again be marketed without prior authorisation. It made clear that better standards and authorisation procedures were needed not only in European states, but also at European Community level.

In 1965 the first European Community pharmaceutical directive (Directive 65/65/EEC) was adopted. It aimed to establish and maintain a high level of protection for public health through rules for development and manufacture of medicines; establishing guidelines for post-marketing monitoring of drug safety; and through establishing safety, efficacy and quality as the sole grounds for market approval. Thus, one can say that the first Community involvement in the European pharmaceutical market had a strong public health policy perspective (protection) but in the meantime it also aimed to establish European standards necessary for the common market.

Ten years later two important directives (75/318/EEC and 75/319/EEC) introduced mutual recognition of the respective national marketing authorisation procedures in Member States and provided the first step towards creating a Community-wide single European market in pharmaceuticals. Directive 75/318/EEC, created the ‘mutual recognition’ procedure, which was intended to enable and speed up free movement of medicinal products within the Community on basis of scientific criteria of quality, safety and efficacy. This new procedure

was facilitated under Directive 75/319/EEC, which set up a Committee for Proprietary Medicinal Products (CPMP), a single authorisation and administration body for the Community market comprising representatives from each of the Member States.

Mutual recognition, also known as the CPMP procedure, encouraged manufacturers –if the manufacturer had an existing authorisation for at least one Member State– to seek simultaneous marketing authorisation for a drug in five or more recipient Member States (out of the then nine Member States), allowing companies to submit application without regulatory staff in every country, thus enhancing smaller national manufacturers to compete more globally. However, the mutual recognition procedure did hardly improve the situation. It caused delays as recipient Member States sought (non-binding) arbitration from the CPMP on nearly every occasion. If arbitration had an undesired outcome for a recipient Member State, it could still refuse authorisation under article 36 of the 1957 Treaty establishing the European Community (TEC), which gives members exception to the free movement rules where public health is at stake. Consequently, the procedure was not popular with industry. Only 41 applications were made in the eight years it was in place and the procedure was mostly used for –for industry less important– generics or 'me-too' products. Of the 41 applications, 28 (70%) received a favourable opinion. The 41 applications led to 175 authorisations and 65 final refusals (Cartwright and Matthews 1991).

Clearly, the CPMP procedure was not being accepted by Member States and unattractive for industry. In 1983, therefore, the EU created the Multi State procedure, in which the minimum number of recipient States was reduced from five to two (out of the then ten Member States). The procedure was introduced via Directive 83/570/EEC, which soon proved troublesome. Although the number of applications submitted rose, it also saw Member States raising objections to all but one of three hundred applications (Abraham and Lewis 2003). It does not come as a surprise that the manufacturers remained sceptical about the advantages of the Multi State procedure. The great majority of applications prior to the introduction of the decentralised procedure in 1995 were submitted via national approval routes (Abraham and Lewis 2000)

The 1985 White Paper 'Completing the Internal Market' provided intentions of the European Commission regarding the completion of the Single European Market. These intentions were strengthened through the Single European Act (SEA) of 1986, which laid out plans to

establish a Single European Market for the movement of all goods, services and capital by 1992. Therefore, in 1987, in another attempt to further rationalise the authorisation process, Directive 87/22/EEC introduced the 'Concertation' procedure. The Concertation procedure, which was compulsory for biotechnology and voluntary for high technology products, forced manufacturers to simultaneously submit their application to the CPMP and one Member State, which acted as a rapporteur. The CPMP could then recommend an EU-wide license, after considering possible objections by other Member States. However, as with the Multi State Procedure, CPMP arbitration was still non-binding and could be ignored by Member States. They both failed to fulfil expectations, although the Concertation procedure was more successful in terms of applications submitted and agreements over labelling (Jones and Jefferys 1994).

Meanwhile, a European restrictive pricing policy was discussed (and successfully opposed and fought by the EFPIA). However, in 1989 the European Commission introduced Directive 89/105/EEC, known as the 'Price Transparency Directive', in order to counter price differentials for medicinal products between the Member States, which were, according to Chambers & Belcher (1994), up to five times on single products' prices. The Price Transparency Directive required the Member States to adopt verifiable and transparent criteria in setting pharmaceutical prices and their inclusion in national health systems. The Directive is limited in its aim: it does not regulate European wide price controls or profit caps, nor does it seek to harmonise rules of the various national reimbursement schemes. However, it could be seen as the first Community involvement into the field of pricing and reimbursement.

Further SEM-relevant legislation with regard to wholesale distribution (Directive 92/25/EEC), classification of pharmaceuticals (92/26/EEC), labelling and packaging (Directive 92/27/EEC), advertising (Directive 92/28/EEC) and patent protection (Regulation 1786/92) followed. Despite this legislation, intra EU price differentials were not reduced. In 1994 the European Commission expressed concerns that part of the pharmaceutical industry in the European Union may be losing global competitiveness, with consequent economic and social cost for Europe (European Commission 1994).

Some of the key actions identified in the 1994 Communication were put into action. On January 1995 a major change took place. CPMP opinions in both the Multi State procedure as the Concertation procedure became binding on Member States as laid down in Directive

93/39/EEC. Member States can only question the opinion if they can prove it has negative public health impact on their populations. To administer these new procedures, with the expert advice from the CPMP, the European Agency for the Evaluation of Medicines (EMEA[12]) was established under Regulation 2309/93 and started operations in February 1995. To mark these changes, the Multi State procedure was renamed the *decentralised* procedure and the Concertation procedure the *centralised* procedure.

In their responses to this 1994 Communication, both the European Parliament (Resolution of 16 April 1996) and the Council (Resolution 96/C 136/04) stressed the importance of working towards a European industrial policy for pharmaceuticals. In their view this could be reached by completing the internal market and by creating a stable and predictable environment in order to protect the health of patients, by ensuring rapid access to the market and by encouraging therapeutic innovation. However, no progress was made after the introduction of these documents.

In 2000, the Commission ordered a detailed assessment of EMEA's procedures and operations, a commitment made with Article 71 of Regulation 2309/93, which was undertaken by external consultants Cameron McKenna and Arthur Andersen Consulting (European Commission 2000). On the basis of this assessment, the Commission drafted a discussion document (European Commission 2001a) which eventually led to the adoption of a proposal for a comprehensive reform of the EU pharmaceutical legislation in July 2001, which is often referred to as 'Review 2001' (European Commission 2001b). The review had the following objectives in mind: guarantee a high level of public health protection for Europeans; complete the internal market in pharmaceutical products; meet the challenges of EU enlargement and rationalise and simplify the system as far as possible.

The proposal for reform particularly concerns Regulation 2309/93, which provides the legislative framework for regulating medicinal products and resulted in Directive 2001/83/EC on human medicines and Directive 2001/82/EC on veterinary medicines (European Commission 2001a, 2001b). Directive 2001/83/EC on the 'Community Code relating to medicinal products for human use' of 6 November 2001 (later amended by the 2004 Directive 2004/27/EC), replaced and consolidated the first pharmaceutical Directive 65/65/EEC with all its relevant amendments, the two 'landmark' directives 75/319/EEC and 75/318/EEC and

[12] EMEA now stands for European Medicines Agency and is referred to as such in the thesis

their respective amendments, and the 1992 Directives on wholesaling (92/25/EEC), classification (92/26/EEC), labelling and packaging (92/27/EEC) and advertising (92/28/EEC).

3.2.2. European Union pharmaceutical policy 2001-2005

EU pharmaceutical policy thus far shows that progress has been made using secondary legislation such as Directives and Regulations, mainly regarding licensing, which eventually led to a high degree of harmonisation of national practises and a centralised licensing procedure under the auspices of the EMEA. In the field of pricing and reimbursement however, the 1989 Price Transparency Directive counts as the single accomplishment of 40 years of Community policy. The Transparency Directive was intended to be the first step towards European regulation of national price and profit control. The Commission never proposed any form of regulation for price controls and has viewed this primarily a national matter. This is not surprising because of various reasons. Firstly, the European Commission's main goal is liberalising the market and is decidedly leaning towards industrial policy. Installing some sort of price control or profit caps is incompatible with this aim. Secondly, even if the Commission had wanted to introduce profit and price controls, there are huge practical problems. Setting the appropriate margin for retail price control is particularly difficult, given the fact that pharmacy costs differ considerably from one Member State to another, as do the methods of retail price control (OECD 2002). Lastly, the 1992 Maastricht Treaty formally established the Principle of Subsidiarity (also see Section 3.4) in EU law, effectively making it even more problematic for the Commission to interfere with national policy.

Summing this up, there is still no SEM for medicines. After some progress, a standstill is reached. This standstill mainly stems from the conflict between the aforementioned Principle of Subsidiarity and the rules of the SEM regulation, i.e. the free movement rules. The former enables Member States to retain the competence to determine national health care policy –and thus pharmaceutical policy– by delimiting the policy competence to the lowest level at which it can be effectively undertaken, while the latter demands the free movement of goods, including pharmaceuticals. What follows is a conflict between Member States who defend the right to set their own prices and take their own reimbursement decisions within their respective system and the European Commission which has the legal duty to liberalise the

market and demands that there be no obstacles to their circulation within the EU. In other words, competing policy objectives and competences exist between national (cost containment) and supranational (market liberalisation and free movement rules) policymakers.

In addition to this standstill, it became clear to the European Commission that the European pharmaceutical industry was 'losing out' on its main competitors, i.e. mainly the USA and to a lesser extent Japan. The 2000 report on 'Global Competitiveness in Pharmaceuticals, a European Perspective', drafted for the Directorate-General for Enterprise, pointed out that Europe is 'lagging' behind in competitiveness in comparison with the USA (Gambardella et al. 2000). Indicators like Research and development (R&D), size of the European industry, size of European pharmaceutical markets and growth rate, show that the European pharmaceutical sector is losing out on its main competitors. The pharmaceutical sector, a high growth and innovation intensive industry, is a main provider of employment, the main contributor to the European trade balance and through its products important for achieving health goals and thus of high strategic and economic importance. National price and profit regulation was said to have protectionist effects on European Pharmaceutical industry and reducing the incentive for innovation.

As an answer to the Pammolli-Report findings, the 'High level group of innovation and provision of medicines' (G10 Medicines Group), was installed in March 2001. The G10 Medicines Group, set up by the then Commissioner for Enterprise Erkki Liikanen and the then Commissioner for Health and Consumer Protection David Byrne, explored possible directions for future EU policy, with achieving the seemingly dichotomous goal of innovation (competitiveness) and provision (accessibility) in the pharmaceutical sector. Although the G10 process integrated a stronger public health perspective through the involvement of DG Health and Consumer Protection, national health ministers and interest groups, it is discussed in this Section as it is mainly driven by the Community's internal market aspirations and as a result has a strong industrial policy perspective. The creation of the G10 group was in recognition that the Pharmaceutical Review on its own would not be sufficient to tackle the competitiveness problems currently faced by pharmaceutical industry. This needed to be accompanied by national action as well. Therefore, in May 2002, the G10 process resulted in a series of recommendations, without direct legislative Community action.

3.2.3 The G10 process

Methodology

The G10 Medicines Group, consisting of health and industry ministers, representatives of pharmaceutical industry and patient groups, worked using the 'Lisbon Method', in which the Commission served as a facilitator to help the members develop 'practical recommendations'. Three working groups were created (provision, Single Market and innovation). These working groups resulted in a consultation paper, containing key issues and broad conclusions, which was issued for public consultation to reach a wider group of stakeholders. The consultation often resulted in critical and conflicting responses. In addition to the consultation exercise, the G10 Medicines Group undertook two other measures to increase transparency: the creation of a special website[13], containing all the documents used, a forum and progress of the G10 Medicines Group process and a programme of workshops to examine specific issues in more detail. The goal of this methodology was to reach consensus –within the G10 Medicines Group– on a recommendation package. This goal led to a final set of 14 recommendations, published and presented to President Prodi on may 2002 (European Commission 2002).

The recommendations

The recommendations concentrate around five areas.

1. Benchmarking
2. Competition, regulation, access and availability in markets
3. Stimulating Innovation and improving the EU science base
4. Patients
5. Enlargement

Benchmarking: competitiveness and performance indicators

1. *The use of Benchmarking*

   The Commission should develop a comprehensive set of indicators, to enable comparisons between the EU and its major competitors as a basis for establishing best practices.

[13] G10 website: http://ec.europa.eu/enterprise/phabiocom/p3.htm

2. *Access to innovative medicines*

The European institutions and Member States should secure better access and availability to innovative medicines through improved licensing-legislation to improve market introduction, and by improving the use of modern telecommunication infrastructure ('telematics') and techniques to facilitate the operation of the Community regulatory system.

3. *Improve timing of reimbursement and pricing negotiations*

With respect for national competence, Member States should try to improve time taken between the actual marketing authorisation and pricing and reimbursement decisions, in order to have procedures that are both effective and ensure speed of access.

4. *Developing a competitive generic market*

The European institutions and Member States need to secure a competitive generic market through improvements in the licensing process. This should be achieved through finding an appropriate balance between providing intellectual property protection for innovative medicines and easy access to the generic market through introduction of a Bolar provision[14]. However, it is still the Member State that determines the desired degree of generic penetration.

5. *Developing a competitive non-prescription market*

In order to develop a competitive non-prescription market, Member States should review, where appropriate, amend mechanisms and concepts for moving medicines from prescription to non-prescription status and should allow the use of the same trademark for the products moved to non-prescription status.

6. *Full competition for medicines neither purchased nor reimbursed by the state*

The Commission and Member States should secure the principle that a Member State's authority to regulate prices in the EU should extend only to those medicines purchased by, or reimbursed by, the state. Full competition should be allowed for medicines not reimbursed by State systems or medicines sold into private markets.

[14] A Bolar provision enables commercial testing, using and making (not selling) of on-patent pharmaceuticals prior to patent expiry. Through this exemption of exclusive patent rights, manufacturers can obtain marketing approval before the patent has expired, and secure a more rapid market access. It is named after a case judged by US courts in Roche Products Inc. vs. Bolar Pharmaceutical Co in 1984.

7. Relative effectiveness

Although mechanisms to establish relative cost and clinical effectiveness primarily are a matter of national competence, the Commission should facilitate exchange of national experience on health technologies (HTA) and new information technologies.

Stimulating innovation and improving the EU science base

8. Creation of virtual institutes of Health

The creation of the European virtual institutes of health should be stimulated, connecting all existing competence centres on fundamental and clinical research into a European network of excellence.

9. Install incentives for research

Commission and Member States should support and co-ordinate the conduct of clinical trials on a European scale and establish a database of trials and clinical research results. They also should put in place an effective policy in terms of incentives, support areas of funding that are not as attractive due to restricted size of the expected market (i.e. orphan and paediatric drugs), and support the development of a biotechnology strategy in Europe (for which the completion of Directive 98/44/EEC on the Legal Protection of Biological Inventions is important).

Patients

10. Enhanced information

The restriction on advertising of prescription medicines to the general public should be continued but there should be no restrictions on advertising of non-prescription and non-reimbursed medicines. There should be a practical and workable distinction between advertising and information through guidelines agreed by both Member States and European Commission.

11. Review of patient information leaflets

Legislation relating to patient information leaflets should be reviewed taking into account views of users as well as regulators of industry.

12. Pharmacovigilance

Systems for post marketing surveillance should be optimised to ensure that co-ordinated processes are in place to gather data on adverse events and patient safety.

13. Funding for patients groups

The Commission should consider providing core funding for European patient groups to enable them to participate independently in the debate and decision making on health matters in the EU.

Enlargement

14. Take full account of enlargement

Although it is difficult to predict the impact of enlargement on the pharmaceutical market, in this recommendation the G10 Medicines Group stresses that the Commission should take full account of enlargement consequences and issues.

In July 2003, the European Commission (2003) welcomed the analysis and approaches proposed by the G10 group in Commission Communication COM (2003) 383 'A Stronger European-based Pharmaceutical Industry for the Benefit of the Patient –A Call for Action'. The Commission divided the G10 recommendation into 5 broad themes –resembling the five themes used by the G10 Group (see table 8). To realise these recommendations, the Commission developed an extensive set of key actions some linking to programmes already in place, and ostensibly put patients' issues on the top of their list:

- Benefits to patients: improving patient information on medicines, strengthening role of patients in public health decision making through support of consumer groups and strengthening European supervision of medicines (pharmacovigilance). Also under this section is the recommendation to review national approaches to cost and clinical effectiveness of medicines.
- Developing a competitive European based industry: examining ways of improving access to innovative medicines, the need to speed up national negotiations on reimbursement and pricing, greater price competition for medicines that are not part of the state sector and measures to develop competitive generic and non-prescription markets.
- Strengthening the EU Science Base: examining ways to develop incentives for research, including the use of virtual institutes for health and biotechnology as an

addition to the 6th Framework Programme for Research and Technological Developments (FP6)[15] already in place.

- Medicines in an enlarged European Union: examining ways how to the challenge of enlargement through providing a level playing field for intellectual property protection and providing support for the accession countries to implement the new legislative framework.
- Member States learning from each other: introducing benchmarking through a set of agreed EU performance indicators (Supply, Demand & Regulatory Framework, Industry Outputs and Macroeconomic factors) as a basis for monitoring the implementation of recommendations and to exchange best practice. It was proposed that this could be linked to work under the Health Monitoring Programme (1998-2003) and activities planned by Eurostat as part of their development of a Systems of Health Accounts.

Table 8 The Commission's adoption of G10 Medicines recommendations

European Commission Communication COM (2003) 383	**G10 medicines recommendations number:**	**Corresponding with G10 medicines theme[16]:**
Benefits to patients	7,10,11,12,13	Patients
Developing a competitive European based industry	2,3,4,5,6	Competition, regulation, access and availability in markets
Strengthening the EU Science Base	8,9	Stimulating innovation and improving the EU science base
Medicines in an enlarged European Union	14	Enlargement
Member States learning from each other	1	Benchmarking: competitiveness and performance indicators

Source: own compilation

The European Commission remained preoccupied with the competitiveness of the European pharmaceutical sector. A distinctive fall in applications for marketing authorisations in 2002 and 2003 led the Commission to believe that there might be a worldwide crisis in innovation in the pharmaceutical sector. Against this background, DG Enterprise commissioned Charles

[15] The 6th Framework Programme (FP6) for Research and Technological Developments (2002-2006) was a collection of the actions at EU level to fund and promote research, leading to the creation of a European Research Area (ERA).

[16] In the G10 report, recommendation 7 concerning 'relative effectiveness' is classified under 'competition, regulation, access and availability in markets'. The Commission, however, schedules it under 'benefits to patients'. This is the only major difference with the G10 and seems to underline the emphasis of the Commission on (supposed) patient benefits even more.

Rivers Associates to undertake a study. This study aimed to investigate: (1) whether there is a crisis in innovation in the pharmaceutical sector; (2) the reasons behind any crisis; and (3) tools available to kick-start innovation.

Outcome of the study was that the recent decline in applications does not reflect a crisis in innovation. Recent history of applications (and the close relationship between applications and authorisations) suggested that a recovery in authorisations was likely in 2004/2005. However, the report came with a range of recommendations broadly in line with the 2000 Pammolli report findings and recent policy proposals in the EU (also see below), concerning faster market access, streamlining the regulatory process and the level of market exclusivity. Furthermore, the report stressed the importance of clearing the (observed) bottleneck of Phase III development (by helping companies to accelerate the process of bringing products to the market) and the importance of improving Europe's attractiveness as a locus of innovation on the medium term (European Commission 2004a).

In 2004, Pammolli et al. published an update of their 2000 report, this time called 'European competitiveness in pharmaceuticals' in which they concluded that their initial findings still apply: 'As a whole, Europe is still lagging behind in its ability to generate, organise, and sustain innovation processes and productivity growth in pharmaceuticals'. The report concluded that the failure of the (continental) European pharmaceutical industry in achieving a substantial productivity acceleration cannot be fully explained by factors which are sector specific, but should also be explained by a relatively low dynamism in Europe in reforming some of its key capitalist institutions (labour and capital markets, education, welfare). Also, the uneven geographical distribution of research activities in pharmaceuticals, together with the observed differences in price levels for innovative drugs and in reimbursement schemes between Europe and the US, as well as across European countries, seem to call for a relaunch of transatlantic dialogue on the political economy of the pharmaceutical industry.

In March 2004, the Directive 2004/27/EEC amended the Community Code relating to medicinal products for human use, which deals with new requirements for the use of Braille in packaging and leaflets. Furthermore, Regulation 726/2004 repealed the well-known Regulation 2309/93 in which the EU market authorisation procedures were laid down, although the general principles of 2309/93 remained in place. It mainly sought to improve the centralised and decentralised procedure through faster procedures, expanded mandatory list of

pharmaceutical products (centralised procedure) and further harmonisation of data protection period (decentralised procedure). Regulation 726/2004 applied from 20 November 2005.

The Commission's unrelenting absorption with the competitiveness of the pharmaceutical industry is maybe best reflected in the installation of the DG Enterprise and Industry unit 'Competitiveness in the Pharmaceuticals industry and Biotechnology'. This unit's overall goal is to promote innovation and competitiveness in biotechnology and pharmaceutical industries, with particular attention to the completion of the Single Market and health and consumer protection. In June 2005, Vice president and Commissioner for Enterprise and Industry Verheugen and Commissioner for Health and Consumer Protection Kyprianou established the Pharmaceutical Forum[17], which involves yearly meetings in the period 2006 up to 2008. The Pharmaceutical Forum follows up on issues sill outstanding from the G10 medicines process and formed three expert groups around the subjects 'Information to Patients', 'Relative Effectiveness' and 'Pricing and Reimbursement'.

The process put forward in the aftermath of the G10 recommendations could be seen as a break from the traditional approach of harmonisation through European legislation (also see table 9) in favour of a more feasible approach of co-ordination of national results and through this, respecting the subsidiarity principle and the national competence. Much will depend on Member States now and their willingness to cooperate. Are they willing to accept coordination and consequently guidelines and benchmarks, not just for industrial matters but for health policy matters?

[17] The Forum is chaired jointly by Vice-President Verheugen and Commissioner Kyprianou. Ministers from each Member State are invited. In addition to Member States, three representatives from the European Parliament are members. The remaining membership is made up of senior representatives of all actors in the pharmaceutical market.

Table 9 A Non-exhaustive list of 40 years of European Community action in the European Pharmaceutical Market (1965-2004)

Year	Important developments	Concerning
1965	Directive 65/65/EEC	Establishing rules for development and manufacture of medicines, guidelines in order to maintain a high level of protection for public health.
1975	Directive 75/318/EEC	Set up a Committee for Proprietary Medicinal Products (CPMP) in order to facilitate 'mutual recognition'.
	Directive 75/319/EEC	Introduction of 'mutual recognition' of respective national marketing authorisation procedures.
1983	Directive 83/570/EEC	Creation of the Multi State procedure, in which the minimum number of recipient States was reduced from five to two.
1985	White paper 'Completing the Internal Market'	Laid down Commission proposals concerning the completion of the internal market.
1986	Single European Act (SEA)	Act laying out plans to establish a Single European Market for the movement of all goods, services and capital by 1992.
1989	Directive 89/105/EEC	'Price Transparency Directive' in order to counter price differentials for medicinal products between Member States.
1992	Directive 92/25/EEC	Wholesale distribution
	Directive 92/26/EEC	Classification
	Directive 92/27/EEC	Leaflets and labels
	Directive 92/28/EEC	Advertising and sales promotion
	Regulation 1786/92	Patent protection
1993	93/39/EEC	CPMP opinions in both the Multi State procedure as the Concertation procedure became *binding* on Member States Introduced as of 1995.
	Regulation 2309/93	Establishment of EMEA. Started operations in February 1995 introduced centralised procedure.
1996	Resolution 96/C 136/04	Call by the European Council for an industrial policy for the pharmaceutical sector in the European Union.
2000	Report 'Global Competitiveness in Pharmaceuticals, a European Perspective' (Pammolli-report)	Report which indicated that the European Pharmaceutical industry is losing out on its main competitors, particularly the United States.
	Release of 'Evaluation of the operation of community procedures for the authorisation of medicinal products'	Cameron McKenna and Andersen Consulting Report on Review of medicines licensing.
2001	Memo/01/267	Reform of European Union pharmaceutical legislation
	Directive 2001/83/EC	Community Code relating to medicinal products for human use.

2002	G10 Medicines report	Final report of the G10 process
2003	COM(2003) 383 A stronger European-based pharmaceutical industry for the benefit of the patient –a call for action	The commission's answer to the G10 recommendations, in which it adopted their views and laid down an extensive set of 'key actions' for the future European Pharmaceutical Market.
2004	Release of report 'Innovation in pharmaceutical sector'	Charles River associates report on a possible crisis in innovation in the pharmaceutical sector, reasons and potential remedies.
	Report 'European competitive-ness in pharmaceuticals	An update of the 2000 Pammolli-report that shows that Europe's pharmaceutical industry is still behind their US counterparts.
	Directive 2004/27/EC	Amending Directive 2001/83/EC on the Community Code relating to medicinal products for human use. Includes changes to the label and package leaflet requirements: Braille on the packaging, and leaflet to be made available in formats for the blind and partially sighted.
	Regulation 726/2004	Laying down adjusted Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

Source: own compilation

3.3 European Union social policy

The European Community's social policies mainly aimed at the workers working across borders and guaranteeing their social security benefits in an increasingly Europe-wide labour market. The potential loss of social security benefits constituted barriers for those segments of the labour force wanting to work abroad. Through the Treaty of Rome, the EEC was committed to 'ensure the economic and social progress of their countries by common action to eliminate the barriers which divide Europe'. What the influence of EU social policy is on the provision of statutory health services (of which pharmaceuticals are part) has to be dealt with in the broader context of social security (of which statutory health services are part) and the historical development of patient mobility. This field of EU policy is the domain of the powerful (when compared to DG Health and Consumer Protection) DG Employment, Social Affairs and Equal opportunities. Although reimbursement levels and decisions are the competence of the Member States, there is a relevant amount of EU legislation and –maybe even more importantly– ECJ rulings that Member States have to adhere to, in case of a patient who decides to seek reimbursement for the costs for health services incurred abroad.

Previously, it was considered a solely private matter if anyone (e.g. a temporary visitor, a long-term resident or a migrant worker) required treatment abroad. In other words, the costs were borne individually, whether or not with some form of travel insurance or other arrangement through the employer in case of a migrant worker. However, in the 1970s, the then European Economic Community recognised that the principle of free movement of people was meaningless if only those who were in full health could take advantage of this freedom (Bertinato et al. 2005).

Therefore, the community set up a social security coordination system laid down in Council Regulation (EC) No. 1408/71 and 574/72[18] which established a series of mechanisms by which individuals can obtain health care abroad based on the principles of free movement of persons. In 2004, Regulation (EC) No. 883/04[19] was adopted, which in time will replace Council Regulation (EEC) No. 1408/71. This new regulation will eventually modernise the framework and incorporate important case law[20].

3.3.1. The European legal frameworks for cross-border health care

In the area of health care, the primary aim of Council Regulation (EC) No. 1408/71 is to guarantee access to care in the State of residence for migrant workers and their families, but Article 22 of Regulation 1408/71 also states the eligibility for reimbursement for treatment in another Member State than the State of residence or affiliation. This eligibility for cross-border health services is subjected to the following conditions:

- Occasional care: when temporarily in another Member State, a person is entitled to (publicly contracted) care becoming medically necessary during their stay. To prove his/ her entitlement in the home state and in order to receive care in the host state, the

[18] Council Regulation (EEC) No. 1408/71 of the Council of 14 June 1971 on the application of social security schemes to employed persons and their families moving within the Community; Consolidated version of 5 May 2005; Council Regulation (EEC) No. 574/72 of 21 March 1972 fixing the procedure for implementing Regulation (EEC) No 1408/71 on the coordination of social security schemes for persons moving within the Community, Consolidated version of 5 May 2005.

[19] Regulation (EC) No. 883/2004 of the European Parliament and of the Council of 29 April 2004 on the coordination of social security systems, OJ L 166, 30.4.2004; however, this regulation has not been fully implemented and therefore Council Regulation (EEC) 1408/71 is referred to in this thesis.

[20] For example, prior-authorisation was addressed to align it with the jurisprudence of the ECJ on 'undue delay' in the Watts Case (Case C-372/04).

patient should carry a European Health Insurance Card (EHIC)[21] and show it to a publicly contracted health care provider in the host state.

- Planned care: patients moving to another Member State specifically to obtain care need to obtain prior authorisation (certified by an E112 form) from their competent institution in their home state and submit it in at the competent authority (depending on Member State e.g. a sickness fund or provider) of the host state. This authorisation has to be given if the treatment is part of the benefit package at home but cannot be given within a medically justifiable time-limit.[22]

It is important to note that under Council Regulation (EC) No. 1408/71 the patient is treated in the host Member State as if he or she is a resident of that Member State. In other words, the reimbursement conditions and tariffs of the state of treatment apply, which will then have to be reimbursed by the payer of the home state.

The situation for cross-border health care changed dramatically from 1998 onwards. The European Court of Justice rulings in the Kohll/Decker and subsequent ECJ cases[23] made clear that national health systems and their available statutory health services do not operate in isolation from other Member States, but also have to adhere to the free movement rules concerning goods and services (see 3.5 for a more detailed discussion of these cases). These rulings created an alternative framework, interwoven with 1408/71 and therefore described here, not based on free movement of persons, but on the free movement of goods and services:

- Concerning *non-hospital services* received abroad, the ECJ ruled that pre-authorisation was not considered necessary, as the ECJ did not regard the need to maintain the financial balance or the quality of the health services as a justification for this 'barrier' to the free movement rules. The court reasoned that it was unlikely that a substantial rise in cross border mobility to obtain non-hospital services abroad would

[21] The EHIC's 'predecessor' was form E111 which had to be submitted in the host state. The EHIC was introduced in 2004 to revise and simplify the coordination mechanism for occasional care by replacing all existing paper forms required for occasional care (E111, E110, E119 and E128).
[22] Following the Watts case (Case C-372/04) the ECJ ruled that in order to refuse an E112 authorisation on the grounds of waiting times, the public health service must establish that the waiting time does not exceed a medically acceptable period having regard to the patient's condition and clinical needs, i.e. no 'fixed' time limit, but rather a waiting time that relates to an individual patient's condition.
[23] Case C-158/96, Kohll; Case C-120/95, Decker; Case C- 368/98, Vanbraekel; Case C-157/99, Geraets-Smits/Peerbooms; Case C-385/99, Müller-Fauré/Van Riet; Case C-56/01, Inizan; Case C-08/02, Leichtle.

occur and threaten the system, since coverage would be limited to the levels and conditions of the country of insurance affiliation.

- In the case of *hospital services*, the ECJ did accept certain barriers to the free movement of health services. Access to hospital services can indeed by subjected to a pre-authorisation (thus an E112 form), considering the importance for Member States to maintain a balanced and accessible hospital services, through a system of planning and contracting. However, authorisation to receive treatment in another Member State may only be refused if the same or equally effective treatment can be obtained for the patient, without undue delay, from a contracted health provider at home.

It is important to note, that non-hospital treatment provided under this legal framework –from now on to be referred to as the 'Kohll/Decker' procedure– will be covered on the terms offered by the state of insurance, as opposed to the state of treatment under the EHIC and E112 schemes. Through its rulings, the ECJ has developed a fairly coherent body of jurisprudence regarding cross-border health services. It aimed to strike the right balance between the social nature of health services and the national competence on the one side, and internal market legislation and the European competence on the other side. It remains to be seen, however, whether the current balance will remain dominant over the next years, as each ruling seems to open up more questions necessitating an interpretation in the form of a new ruling. For example, there is no European definition of 'hospital' or 'non-hospital' treatment and 'undue delay', which may well lead to valid differences in interpretation, which opens up the possibility for patients (as seen before) to start legal proceedings in order to receive pre-authorisation for care that may not be covered or available and reimbursed at home.

3.3.2. Access to cross-border pharmaceuticals

The above described parallel existing frameworks together provide four 'options' of which three can be used to obtain reimbursement for a Prescription Only Medicine (POM) abroad[24] (see figure 6).

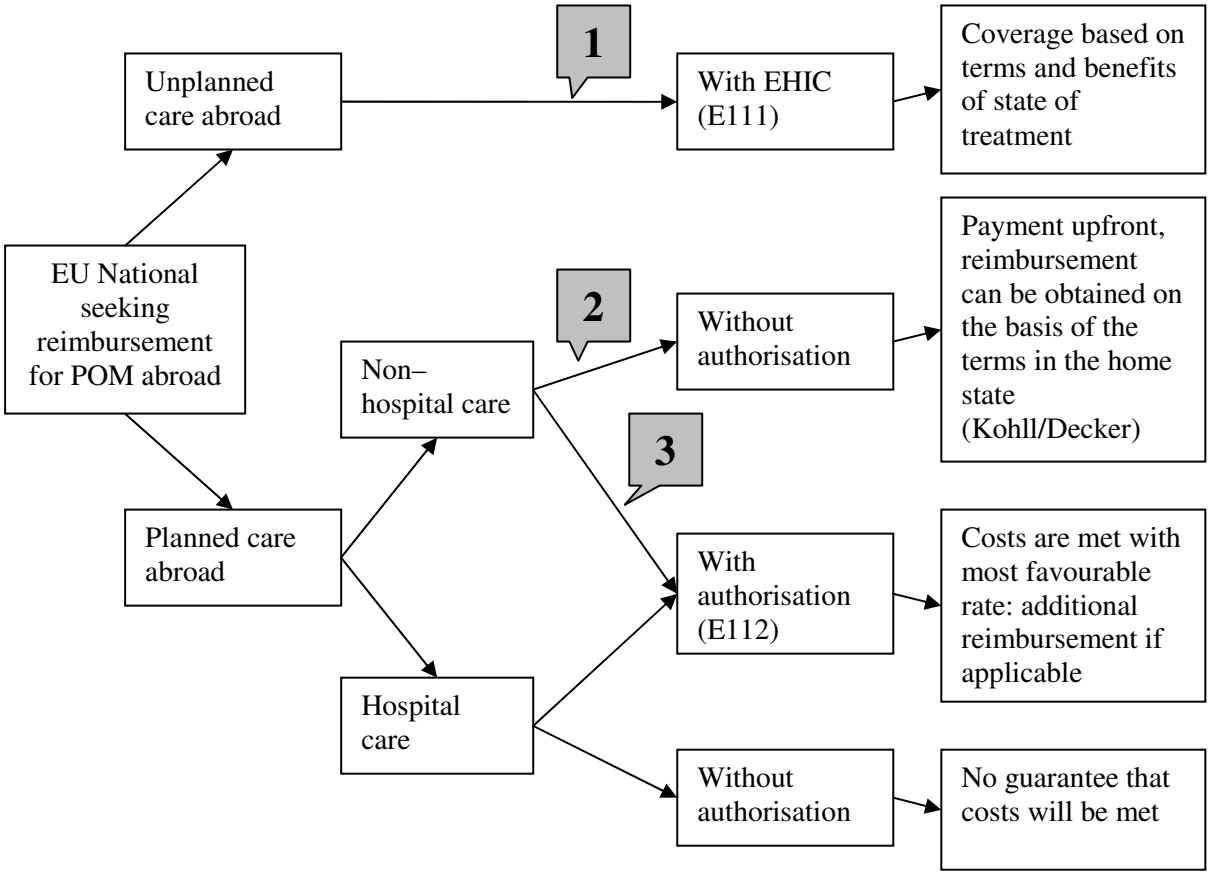
[24] Hospital treatment will often include pharmaceutical treatment, however in this thesis the focus is on extramural provision of pharmaceuticals that citizens can obtain individually. Furthermore, one could interpret cross-border contracts, which are bilateral agreements mostly taking place between health insurers and health care providers as a fifth option to receive cross-border care. Both are, however, predominantly beyond the scope of this thesis.

1. The first option, using the EHIC card, only applies to occasional care on a temporary stay abroad (e.g. holidays). The patient is treated in the host Member State as if he or she is a resident of that Member State which implicates that reimbursement conditions, benefit basket and tariffs of the state of treatment apply. This option could motivate patients to go abroad, for example on holidays or a daytrip, and feign that an immediate need for a certain pharmaceutical treatment occurs that is not provided or reimbursed in the home system. The potential to 'shop' around for pharmaceuticals with an EHIC is considerable, although distances, travelling costs and information on what is available constitute severe barriers in its use.
2. The second 'option', enabled through the ECJ rulings, is planned non-hospital care abroad without using an authorisation. In this case, patients are restricted to the terms and benefits of the home state. This means that they cannot obtain reimbursement for pharmaceuticals abroad that are not included in the benefit basket at home, i.e. the positive list for pharmaceuticals. This also implies that possible higher tariffs in the state of purchase will not be covered by an additional reimbursement (as under EHIC and E112). This is of course a rather theoretical situation as it seems unlikely for a patient to go abroad for a pharmaceutical that he can obtain in the home state without extra costs. Although, under certain circumstances, for example in case of a foreign pharmacy that is much closer than the pharmacy in the home state, the patient may settle for a (small) out-of-pocket payment. If, however, this particular pharmaceutical is cheaper abroad, the patient would in theory be entitled to receive reimbursement up to the higher home state tariff and possibly make a profit[25] or bypass a co-payment. Whether this option is used in practice and known to the public is hard to say as no data or case studies are available. Another interesting development in this regard is the increasing number of internationally operating internet pharmacies that make an (expensive) journey abroad unnecessary. However, there are many potential obstacles for this practice to develop. Some pharmacies will not (or are not permitted) to recognise a foreign prescription, although this may change in the future when a new health services directive will likely also contain mutual recognition of prescriptions. There still exist differences in labelling language, pharmaceuticals on the market and the way that Member States enable internet pharmacies, even though this may violate European (Case) Law.

[25] This is the result of the Vanbraekel ruling (Case C- 368/98)

3. With the third 'option' the patient seeks authorisation to get a reimbursed pharmaceutical abroad. When granted, the patient should be eligible to receive reimbursement at the most favourable rate – the home state rate or the host state rate. This option could be used to obtain reimbursement for pharmaceuticals that are not covered at home, but the authorisation may likely be refused. If a consumer seeks reimbursement for pharmaceuticals that are also provided at home, a positive authorisation decision seems very unlikely in case of a more expensive rate than at home.

Figure 6 Assumption of health care costs abroad, marked with number (1-3) the options that may include (individually purchased) pharmaceuticals



Source: Adapted from 'Assumption of healthcare abroad' chart by DG Employment, Social Affairs and Equal opportunities[26]

[26] See: http://ec.europa.eu/employment_social/social_security_schemes/healthcare/e112/pdf/schema_en.pdf

The above described options, some more hypothetical or theoretical than others, have in common that they are not very well-known to the public, providers and partially also payers, which is mainly due to lack of information. It seems though, that there is potential for patients to obtain reimbursed medicines that are not included in the state of insurance, mainly through using the EHIC. In addition, there seems to be a possibility to make a profit if (the also in the home state provided) pharmaceutical is cheaper abroad, mainly through using the Kohll/Decker procedure. In other words, there may be a financial incentive to seek out those pharmaceuticals that are reimbursed at home but are available and cheaper abroad. This practice could still be considered illegal depending on national framework, and it seems that there is still a need for further clarification, which may be given in the next years provided there are ECJ rulings dealing with cross-border pharmaceuticals.

3.4 European Union health policy

The European Union's involvement in health policy and health care services has always played a relatively minor role in the course of European integration. As stipulated in Article 152 of the Treaty Establishing the European Community (TEC), Community action in the field of public health shall fully respect the responsibilities of the Member States for the organisation and delivery of health services and medical care. Furthermore, it is widely accepted that health care services are subject to the subsidiarity principle. Nevertheless, there is a considerable amount of EU legislation mainly emanating from the implementation of non-health EU policies that has strong remit over several topics relevant to governing, financing, and delivering health services (e.g. medical devices, public procurement and mobility of health professionals). With regard to health services –and thus pharmaceuticals– the 1992 Maastricht Treaty (formally the Treaty of European Union), which reformed the existing Treaties and the Treaty establishing the European Community (TEC) in particular, expanded the EU's mandate on health policy (see table 10) with two new provisions.

Table 10 The EU's mandate on health policy in the Treaty Establishing the European Community.

Article, new version (since Amsterdam[27] treaty)	Article, old version (Maastricht treaty)	Contents/ significance for public health
3 par. 1 (p)	3 (o)	A contribution to the attainment of a high level of health protection
30	36	Restriction of free movement of goods on the grounds of health
39 par. 3	48	Restriction of free movement of workers on the grounds of public health
46 par. 1	56	Restriction of the right of establishment on the grounds of public health
95 par. 3	100 (a)	Attainment of a high level of health protection in the approximation of laws
95 par. 6	100 (a)	Extension of the approximation period in the absence of danger for human health
95 par. 8	100 (a)	Member States obligation to notify specific public health problems in the field which has been subject of prior harmonisation matters
137	118	Improvement in particular of the working environment to protect workers' health and safety
140	118c	Prevention of occupational accidents and diseases
152	129	Public health competences
153	129a	Health protection as part of consumer protection
174 par. 1	130 (r)	Protecting human health as part of environmental policies
186	135	Including public health provisions to the provisions on the association of the overseas countries and territories

Source: Wismar et al. (2002)

First, article 3(o) empowered the Community to 'contribute to the attainment of a high level of health protection' for its citizens. Secondly, Article 129 also ensured a high level of health protection in the implementation of all Community policies and activities and outlined specific areas of competence for this objective, namely the prevention of diseases, through promoting research into their causes, their transmission and their prevention, and through encouraging cooperation between Member States. These two provisions were renewed and

[27] The Amsterdam treaty (1997) was not the last amendment. The TEC was last amended by the Treaty of Nice (2001), which entered into force 1 February 2003. The Treaty of Lisbon, signed on December 13, 2007 amends the existing treaties of the European Union (EU) due to come into force in 2009, if successfully ratified by all European Union member states.

renumbered through the 1997 Amsterdam Treaty into Article 3 par. 1 (p) and Article 152 respectively.

The limitations of the Community sphere of competence are set out in the subsidiarity principle (Article 5 of the TEC), which was established in EU law by the Treaty of Maastricht (1992) and entered into force on 1 November 1993. The subsidiarity principle can be applied only to non-exclusive Community competences (i.e. where shared competence exists, such as public health) and to legislation introduced for the first time. The present formulation, last amended by the Treaty of Nice (2001), entered into force on 1 February 2003, and states:

> *'In areas which do not fall within its exclusive competence, the Community shall take action, in accordance with the principle of subsidiarity, only if and in so far as the objectives of the proposed action cannot be sufficiently achieved by the Member States and can therefore, by reason of the scale or effects of the proposed action, be better achieved by the Community. Any action by the Community shall not go beyond what is necessary to achieve the objectives of this Treaty.'*

It makes clear that the Community can only become active when their objectives cannot be achieved by the Member State (the sufficiency criterion), and when Community action brings added value over and above what could be achieved by the Member State (the benefit criterion).

With regard to EU health competences, the subsidiarity principle is visible in Article 152 of the TEC. It states (paragraph 4c):

> *'…excluding any harmonisation of the laws and regulations of the Member States.'*

and (paragraph 5):

> *'Community action in the field of public health shall fully respect the responsibilities of the Member States for the organisation and delivery of health services and medical care.'*

Therefore, most Member States have assumed that health services fall within their spheres of competence, on the basis of Article 152 of the TEC. However, it became increasingly apparent that EU policies (e.g. competition law, advocating the Four Freedoms) do interfere with Article 152, i.e. may not necessarily respect the 'responsibilities of the Member States' regarding their respective health systems. As far as a European level health policy is concerned, the competence is rather confined to public health policy, advocated by the Directorate General for Health and Consumer Protection, which is also commonly referred to as DG SANCO[28]. Examples include preventing human illnesses and diseases as well as food safety. Also, DG SANCO is leading efforts to clarify (without specific legal action) the framework for cross-border care, as discussed in Section 3.3. However, its influence on pharmaceutical markets and provision is small as compared to DG Enterprise.

3.5 The European Court of Justice (ECJ)

The European Court of Justice (ECJ) was set up in 1952 in Luxembourg. It has the last word on matters of EU law so as to ensure equal application across the European Union member states. Each Member State appoints one judge for a renewable term of six years. Through its interpretations of Community law, the ECJ wields considerable influence on the complicated interplay between European Union, Member States and health services, as well as market liberalisation relevant topics such as parallel importing, repackaging, intellectual copyrights and re-branding. National differences as to the degree and sort of pharmaceutical market regulation may prove vulnerable to litigation, as examples in this thesis underscore (e.g. in the distribution of pharmaceuticals). To discuss the whole body of case law concerning the various topics affecting the pharmaceutical market is beyond the scope of the thesis. Instead, this Section focuses on the Court's decisions in cross-border health care, which have significant effect on cross border provision of health (also see Section 3.3), and some illustrative examples of pharmaceutical market liberalisation.

[28] From the French words Santé (Health) and Consommateurs (Consumers).

3.5.1 The ECJ and cross-border health services

Three important ECJ judgements, in this respect, with great impact on the organisation of national health care are the ECJ ruling (1998) in the cases Kohll (C-158/96) and Decker (C-120/95); the ECJ ruling (2001) in the Geraets-Smits/Peerbooms (C-157/99) and Vanbraekel (C-368/98) cases; and the ECJ ruling (2003) in the Müller-Fauré and Van Riet (C-385/99) cases[29].

Mr Kohll and Mr Decker, both Luxembourg nationals, were refused reimbursement by their Luxembourg health insurance. Mr Decker sought reimbursement for a pair of spectacles (goods) that he had bought in Belgium using a prescription from a Luxembourg ophthalmologist, whereas Mr Kohll demanded reimbursement for a dental treatment (services) his daughter had received in Germany. Both had not obtained a pre-authorisation from their home insurance institution as requested under the E112 procedure. In the Decker case, the court affirmed that national security schemes should also respect article 28 of the EC Treaty on the free movement of goods. In the Kohll case, the ECJ concluded that the requirement of prior authorisation constituted a violation of article 49 and 50 of the Treaty, which ensure the free movement of services. A refusal, the ECJ continued, could only be justified on the grounds of maintaining a balanced medical service accessible to all, guaranteeing the financial balance of the social security system or on overriding reasons in the general interest (e.g. health protection). The ECJ found none of the above justifications for a refusal applicable, as reimbursement at the level of the home state would in no way threaten the financial balance or the quality of the health services in the home state.

The ruling in the Kohll and Decker cases sparked intense political and scientific debate on the meanings and implications of these rulings. As many open questions remained, e.g. on the scope (whether it includes hospital care) and implications for national health systems, it was evident that there was a need for further clarification, which was soon to be provided by the ECJ in its rulings in the cases Geraets-Smits/Peerbooms and Vanbraekel, all concerning the reimbursement of hospital costs incurred in another Member State than the home state.

[29] This list is non-exhaustive. More recent rulings dealing with border crossing health services which affirm and clarify the previous rulings include e.g. Case C-56/01 (Inizan), Case C-08/02 (Leichtle), C-145/03 (Keller) and Case C-372/04 (Watts).

Dutch citizens Mrs Geraets-Smits and Mr Peerbooms were both refused reimbursement by their Dutch sickness funds for the costs of their hospital treatment abroad for multi-disciplinary Parkinson treatment in Germany and 'experimental' coma patient treatment in Austria respectively. Both had not obtained prior authorisation for these –in the Netherlands unavailable– treatments and tried using the procedure based on the free movement of services established in the Kohll case to get a refund after returning home. The ECJ ruled identically in both cases, drawing on previous case law and reiterating that hospital treatment is a 'service' in the sense of the EC treaty and through stating that the Netherlands had violated the free movement rules by refusing authorisation. However, the ECJ accepted that a Member State can justify certain restrictions for treatment through a pre-authorisation if such a restriction is necessary in order to maintain a balanced medical and hospital service accessible to all and to guarantee the financial balance of the social insurance system. The ECJ then continued to elaborate on what constitutes a fair and proportional pre-authorisation procedure, stating: 'Authorisation to receive treatment in another Member State may be refused only if treatment which is the same or equally effective for the patient can be obtained without undue delay from an establishment with which the insured person's insurance has an agreement'.

Mr Vanbraekel tried to obtain reimbursement for orthopaedic surgery his late wife Mrs Descamps, a Belgian resident with Belgian health insurance, received in a French hospital for which she was wrongfully denied authorisation, as a Belgian court would conclude after her return to Belgium. The question that faced the Belgian court was whether she should be reimbursed at the Belgian tariff (as the Kohll ruling would imply for treatment without authorisation), which was significantly higher, or the lower French tariff, as Council Regulation (EEC) No. 1408/71 implies. Eventually the ECJ was consulted, which ruled that lower rates of reimbursement for treatment delivered abroad can discourage people from applying from authorisation abroad and thus medical treatment abroad. Hence, a violation of the free movement rules and, therefore, additional reimbursement covering this difference must be granted to the insured.

This jurisprudence was reaffirmed in the Müller-Fauré/Van Riet judgment of 13 May 2003, concerning the reimbursement of orthodontic treatment outside the Member State of affiliation without prior authorisation. The court made clear that patients are generally entitled for reimbursement for non-hospital services (no need for prior authorisation), whereas for hospital services, a pre-authorisation may be justified. In the judgement, the ECJ once more

explicitly states the conditions that Member States must fulfil in order to ensure that their health care systems are compatible with Community law.

These rulings created a parallel framework to meet costs of health services incurred in another Member State. The original framework, i.e. the procedures established under EC Regulation 1408/71, which includes procedure E112 for planned care and procedure E111 (now the European Health Insurance Card, 'EHIC') for care that becomes medically necessary during an occasional stay, was initially set up to facilitate the free movement of migrant workers. Hence, the procedure was based on the free movement of persons. The new framework, which evolved in the aftermath of the 'Kohll/Decker' case, is based on the free movement of services and goods.

The cases made visible a latent contradiction in the Treaties: free movement of goods and services, but a de facto exclusion of medical goods and services from these principles, as Member States still organise their own social security systems, with country specific conditions. The ECJ ruled that the free movement rules regarding services and goods also apply to the health services in the European Union and that Member States should facilitate this. However, the ECJ also made clear that public health and social security remain the preserve of Member States from a legal as well as a political perspective[30]. The result is a rather complicated framework for reimbursement of cross-border services (see Section 3.3.1) especially from the perspective of the European citizen. Nevertheless, these ECJ rulings increased the opportunities for European citizens to receive reimbursed health care goods (pharmaceuticals) and services (prescriptions, pharmacy services) across borders.

3.5.2 The ECJ and pharmaceutical market liberalisation

The ECJ rulings have been encouraging parallel importing, which resulted in removing divergent national intellectual property rights regarding copyrights, trademarks, and patents. Furthermore, unnecessary national licensing regimes that prevent generic competition have been challenged by the free movement rules. In absence of harmonisation measures, the ECJ

[30] In its judgement in *Smits and Peerbooms* (C-157/99) of 12 July 2001, the court recalled that 'according to case law, Community law does not detract from the power of the Member States to organize their social security systems. In the absence of harmonisation at Community level it is therefore for the legislation of each Member State to determine the conditions concerning the right or duty to be insured with a social security scheme. Nevertheless, the Member States must comply with Community law when exercising that power' (paragraphs 44-46 of the judgement).

in general has been reluctant to act against national rules and regulations regarding price and profit regulation as well as reimbursement (selective lists). Ironically, the price differentials resulting from national divergence keeps parallel trade attractive. Also, Member States are free to determine selling methods, provided that they do not discriminate against imported products (ECJ 1995). However, an ECJ ruling challenged the Commission's ability to force the pharmaceutical industry to provide unlimited volumes of medicines to parallel importing wholesalers when it overturned a 1996 European Commission fine worth ECU 3 Million on the Bayer Group for limiting the supply of Adalat. In the period 1989-1993 the retail price of Adalat (a cardio-vascular drug) was approximately 40 per cent lower in France and Spain than in the UK. This motivated French and Spanish wholesalers to export large quantities of the pharmaceutical to the UK, leading to losses up to €115 million for the British subsidiary. The Bayer Group countered this development by reducing the supply of medicines to Spanish and French wholesalers. The ECJ ruled that the Commission had failed to prove a violation of European competition law as there was found no evidence of an agreement between Bayer and its Spanish and French wholesalers to limit parallel exports of Adalat to the UK.

However, a review undertaken by Hancher (2004) makes clear that in general the ECJ has been unwilling to reverse its pro-internal market, pro-parallel import view especially where it concerns unnecessary obstacles to free movement as a result of nationally divergent property rights. This may be at odds with the G10 process, which acknowledges the importance to industry of property rights and aims to find an appropriate balance between providing intellectual property protection for innovative medicines and easy access to the generic markets.

3.6 European Medicines Agency (EMEA)

The EMEA is responsible for the coordination of the scientific resources that evaluate and supervise medicinal products for both human and veterinary use. Overall there have been three procedures for mutual recognition of marketing authorisation by Member States to this date: the CPMP procedure (1976-1985), the Multi-State procedure (1985-1995) and the decentralised procedure since 1995. The first two were very similar to each other and represent what is often characterised as the 'weak' European regulatory state, and were not overly successful in terms of applications admitted. Major changes occurred in 1995, with the constitution of the decentralised procedure, in combination with the centralised procedure

through the EMEA, which is often characterised as the 'strong' European regulatory state (Abraham and Lewis 2000). These changes mark the beginning of a revolution in European pharmaceutical regulation and made market authorisation increasingly the responsibility of the London-based EMEA. In 2004, adjustments were made to the centralised and the decentralised procedure through EC Regulation 726/2004, which repealed the well-known EC Regulation 2309/93, and aims to provide –in the EMEA's own words– 'a more robust, modern and effective regulatory framework for pharmaceuticals in Europe' (EMEA 2005).

Among the changes made to the centralised procedure are: an expanded list of products for which the centralised procedure is mandatory (in addition to new biotechnology and orphan drugs all new products indicated for treatment of AIDS, cancer, diabetes and neurodegenerative diseases); accelerated procedures through shortened deadlines in the different steps of the procedure; 'fast track' procedures for products of major interest to public health and therapeutic innovation; and the European Medicines Agency's role as a scientific advisor will be strengthened, i.e. it may request the European Commission to impose financial penalties on the authorisation holders.

For the mutual recognition decentralised procedure some important changes are: harmonisation of the data protection period with the period provided for the centralised authorised products, i.e. 10 years, with a possibility for a one year extension under certain conditions; improvement of the procedure, i.e. definitions, legal status; and the arbitration mechanism applicable when Member States disagree over a certain authorisation will be improved by ensuring that the objections related to the serious risk of public health are evaluated properly and that necessary follow up measures are taken.

The centralised drug approval through the EMEA procedure has been reasonably successful and will include generic products in the future. Approval of a drug requires acceptance in al other EU Member States. In the decentralised (national) process a company can apply for approval in one Member State. When it receives approval it can –with the expectation of quick authorisation– apply to the market in other Member States. In case of an objection by a Member State, the EMEA solves the dispute.

Despite its relative success there has been criticism too. Concerns have been raised about the review process, which supposedly approves drugs that may not have much added clinical

benefit despite their higher prices (Mossialos et al. 2004). Consequently, approved drugs are not likely to meet the expectations of patients who believe that these new drug signify substantial improvements in treatments (Garattini and Bertele' 2002).

Furthermore, there are concerns about the operation of the EMEA (Garattini and Bertele' 2004). First, the EMEA is regulated by DG Enterprise, and not by DG Health and Consumer Protection, which objectives would perhaps be more aligned with the interests of patients and less with the interests of industry. Secondly, while EMEA and decentralised national licensing agencies primarily are financed through fees from industry for market authorisation, it can provoke competition for funds. Ideally, the decentralised route should become obsolete, taking away the competition. In addition to this, the European Commission recently suggested that the management board of the EMEA should include representatives from the pharmaceutical industry, providing a possible source for conflicts of interest.

The EMEA does not have an internal staff capable of carrying out evaluations of submitted products, as for example its US 'counterpart', the Food and Drug Administration (FDA). Instead, it contracts national medicine agencies to perform the evaluation and report back their findings. Companies can nominate a national agency when applying via the centralised procedure, which may lead them to choose those more likely to give their product a favourable report (Garattini and Bertele' 2001). This practice could stimulate national agencies to compete with other agencies on rapid authorisation and favourable reports.

All these factors contribute to the fact that the EMEA has been accused of favouring industry in its operations. An alleged swift approval rather than strict assessment as a prime objective has been criticised by various authors (e.g. Abraham and Lewis 2000; Bertele' and Li Bassi 2004; Garattini and Bertele' 2001, 2004).

4 NATIONAL PHARMACEUTICAL POLICIES IN THE EU

The national pharmaceutical market forms an important part of health care systems not only in economic terms but also in terms of public health. The national regulatory mechanisms in Europe were put in place in the aftermath of the Thalidomid tragedy –in analogy with the European Community developments in the early 1960s– to prevent a repetition. In the early years, these regulatory systems mainly safeguarded the quality and accessibility of pharmaceutical provision, but as early as the 1980s containment of pharmaceutical expenditures became more and more a policy objective in European states. The rising expenditures on drugs put pressure on the national health budgets and pose a threat to the financing and accessibility of health care. Usually faster growing than GDP and the health sector as a whole (see table 11), the pharmaceutical sector has been subjected to many national cost containment strategies.

Table 11 Pharmaceutical expenditures in several EU Member States (1985-2005)

	Total expenditure on pharmaceuticals (% of total health expenditure)					**Total expenditure on pharmaceuticals (% of GDP)**				
Year	**1985**	**1990**	**1995**	**2000**	**2005**	**1985**	**1990**	**1995**	**2000**	**2005**
Austria		9.0	9.2	11.9	12.0		0.8	0.9	1.2	1.2
Belgium	15.7	15.5	16.7		17.1	1.1	1.1	1.4		1.8
Czech Rep.		21.0	25.1	23.4	25.1		1.0	1.8	1.5	1.8
Denmark	6.6	7.5	9.1	8.8		0.6	0.6	0.7	0.7	2.0
Finland	9.7	9.4	13.0	15.2	15.8	0.7	0.7	1.0	1.1	1.3
France	16.2	16.9	15.0	16.5	16.7	1.3	1.4	1.6	1.7	1.9
Germany	13.8	14.3	12.9	13.6	15.1	1.2	1.2	1.3	1.4	1.6
Greece		14.3	15.7	17.8	18.5	1.0	0.9	1.4	1.4	1.7
Hungary			25.0		30.5			1.8		2.6
Italy		20.3	20.7	22.0	20.3		1.6	1.5	1.8	1.8
Luxembourg	14.7	14.9	12.0	11.0	8.4	0.8	0.8	0.7	0.6	0.7
Netherlands	9.3	9.6	11.0	11.7		0.7	0.8	0.9	0.9	
Poland					28.0					1.7
Portugal	25.4	24.9	23.6	22.4	21.6	1.5	1.5	1.8	2.0	2.2
Slovak Rep.				34.0	31.9				1.9	2.3
Spain	20.3	17.8	19.2	21.3	22.4	1.1	1.2	1.4	1.5	1.9
Sweden	7.0	8.0	12.3	13.8	13.7	0.6	0.7	1.0	1.1	1.3
UK	14.1	13.5	15.3			0.8	0.8			

Source: OECD Health Data (2008)

The degree to which cost containment measures are adopted reflects how much weight is awarded to industrial policy (e.g. nourishing a science base, employment, and strategic issues), public health policy (e.g. safe medicines, patient access, high quality preparations and

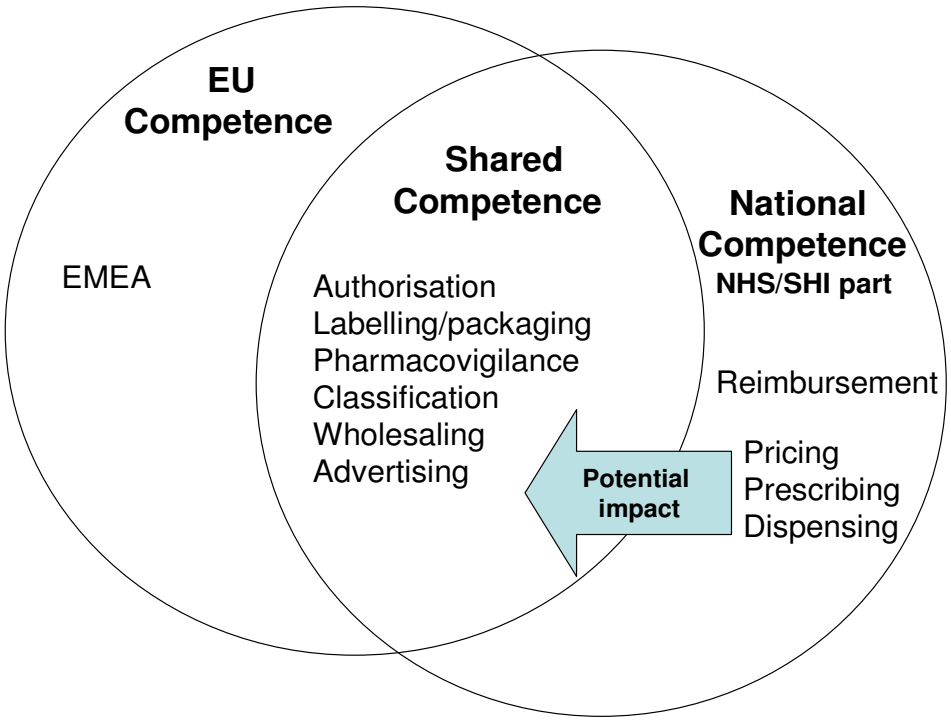
innovative cures) and health care policy (e.g. cost containment, generic promotion, cost effective medication) objectives. But now even Member States like Germany and the UK – which support strong industry and historically have been more willing to make a trade off in favour of industrial policy– cutting back on pharmaceutical expenditures made it onto the national agenda.

Before a medicine gets dispensed, it has to be admitted to a national market through the responsible authorisation agencies; this can be achieved through the EMEA (centralised procedure) or through a national medicine agency (decentralised procedure and exclusively national procedure). As soon as the product is licensed, various national regulations –often transposed European directives– apply to the medicine, ranging from issues concerning packaging, advertising, and distribution to pharmacovigilance. It is important to note, therefore, that referring to 'national policy' in this regard may be misleading, as the actual policy is the sum of transposed EU Directives and national regulation, as will become clear in the following Sections. Next, a decision has to be made whether the pharmaceutical will be covered under the respective Member States' health insurance scheme. In principle, most Member States operate systems of universal public coverage, i.e. coverage for the entire population, defined by legal residence or citizenship. In most EU27 Member States this is accomplished through a contribution-based Social Health Insurance system (SHI, e.g. Austria, Belgium, Czech Republic, Estonia, France, Germany, Luxembourg, the Netherlands, Slovakia and Slovenia) or a tax-based National Health Service (NHS, e.g. UK, Sweden, Ireland, Italy, Latvia, Poland, Portugal and Romania)[31]. This 'reimbursement decision' is a crucial decision for industry. If their products are not reimbursed, patients are –because of high costs– not as likely to use it, which means that they will not be able to realise a positive financial return on their investment. After admission to the benefit basket, more regulation under the respective health scheme applies to the pharmaceutical, e.g. measures like reference pricing and co-payments. Furthermore, there is regulation that does not directly concern the pharmaceutical, but seeks to bring down pharmaceutical expenditures by influencing the prescriber (GP/physician) and pharmacist.

[31] In fact, more precisely speaking, each country has a unique mix of sources for health care revenues that exist of both general taxes and social contributions. Furthermore, some systems cannot be strictly described as systems of universal insurance; for certain population groups, the primary mode (or part) of cover for health care is substitutive Voluntary Health Insurance, e.g. in Ireland and Germany.

International studies use various ways to categorise pharmaceutical policies: price-measures versus volume-measures, direct versus indirect measures, demand side versus supply side measures or coercive versus non-coercive measures. However, these distinctions are often used to describe national cost containment strategies Therefore, in order to get a more coherent impression of national pharmaceutical frameworks, the measures and regulatory approaches are discussed at the appropriate level as depicted in figure 7.

Figure 7 Competences in the national pharmaceutical market



The first Section of this Chapter will deal with regulation that applies to the entire national pharmaceutical market. This contains, basically following the pharmaceutical down the value chain: marketing authorisation (licensing), pharmacovigilance, classification, distribution and advertising. These issues are a shared competence between the European Union and the Member State. The second and third Sections will discuss the various national pharmaceutical regulations and measures under the respective SHI or NHS schemes in the European Member States, such as pricing and reimbursement. These will be divided into measures with a potential impact on the entire pharmaceutical market (Section two) and into measures that only have influence within the system (Section three). Making such a distinction is useful, because it makes visible the areas of shared competence, where the Community can become active, albeit in accordance with the principle of subsidiarity. Within their respective health

system, in general, the competence lies with the Member State, following Article 152[32]. However, national regulation that has impact on the entire national health market (see arrow in figure 7) could also fall within the sphere of competence of the European Union (e.g. pricing regulation that affects non-reimbursed medicines). This implies a field of shared competence. It is exactly in these fields that the EU has used its competence and might possibly use it in the future. This Chapter concludes with a Section assigned exclusively to pharmaceutical policy in the new Member States. Its significantly different historic background and recent Western style reforms warrants a more thorough look into its development and reform processes.

4.1 Regulation for the entire national pharmaceutical market

The dissonance between the industrial policy-leaning European Commission and health policy-leaning Member States, force Member States to use the principle of subsidiarity to ward off European regulation contradicting their respective views. Although Member States hold a strong regulatory hand on their pharmaceutical market, there is still a relevant portion of issues, in which the EU is the dominant party. The EU regulatory framework, which aim is to promote the Single European Market, has strong remit over issues such as manufacturing, authorisation, labelling/packaging requirements, advertising rules, wholesale distribution and patent protection. This is achieved through Directive 2001/83/EC[33], the 'Community Code relating to medicinal products for human use', hereafter to be referred to as 'Community Code', which integrates many of the previous pharmaceutical Directives (see Section 3.2). The contents and scope of the Community Code are laid down in table 12. Member States have regulations in place on these issues, but their authority in these matters has been gradually overtaken through these directives, which have to be transposed in their legal framework in order to further harmonise pharmaceutical legislation.

[32] 'in general', because, as seen before, Member States' organisation of the health system must still respect the Four Freedoms. Therefore, the national systems are not completely immune to Community influence.
[33] Directive 2001/83/EC, later amended by Directive 2004/27/EC, replaces and consolidates the first pharmaceutical Directive 65/65/EEC with all its relevant amendments, the two 'landmark' directives 75/319/EEC and 75/318/EEC and their respective amendments, and the 1992 directives on wholesaling (92/25/EEC), classification (92/26/EEC), labelling and packaging (92/27/EEC) and advertising (92/28/EEC).

Table 12 Community Code

Directive 2001/83/EC on the Community Code relating to medicinal products for human use	
Title I	Definitions
Title II	Scope
Title III	Placing on the market
Title IV	Manufacture and importation
Title V	Labelling and package leaflet
Title VI	Classification of medicinal products
Title VII	Wholesale distribution of medicinal products
Title VIII	Advertising
Title IX	Pharmacovigilance
Title X	Special provisions on medical products derived from human blood and plasma
Title XI	Supervision and sanctions
Title XII	Standing Committee
Title XIII	General Provisions
Title XIV	Final Provisions

4.1.1 Market authorisation

In 1995, the establishment of the European Medicines Agency (EMEA) and the centralised procedure meant a huge change for the authorisation of medicines in the European Union (see also Chapter 3). It leaves three options for pharmaceutical companies that seek market authorisation in a Member State: the centralised and the decentralised procedure for EU-wide authorisation, and the 'old' exclusively national procedure.

The centralised procedure

The *centralised* procedure is compulsory for new biotechnology products, orphan drugs and all new products indicated for treatment of AIDS, cancer, diabetes and neurodegenerative diseases. The application is submitted directly to the EMEA and is checked whether it is according to all necessary requirements. If so, the EMEA validates the application and the Committee for Medicinal Products for Human Use (CHMP)[34], part of the EMEA, selects two rapporteurs to assess the application. These rapporteurs are appointed individual members of the CPMP and take into account the preference of the applicant. The rapporteurs will act as coordinator of the assessment report and contact person for the applicant. At the conclusion of the scientific evaluation, undertaken within 210 days, the opinion of the full membership of the CHMP is transmitted to the European Commission to be transformed into a single market

[34] The Committee for Medicinal Products for Human Use (CHMP) was formerly known as the CPMP, Committee for Proprietary Medicinal Products (see Chapter 3).

authorisation for the whole EU, published in the Official Journal of the European Communities. After the product is licensed through the central procedure, the CHMP is responsible for pharmacovigilance, until the product is available on the market.

The decentralised procedure

The *decentralised* procedure (or mutual recognition procedure) applies to the majority of conventional medicinal products and is based upon the principle of mutual recognition of national authorisations, granted by national marketing authorities[35]. Through this procedure, the market authorisation for one European Member State can be extended to one or more other Member States identified by the manufacturer. When problems occur between Member States about the recognition of the authorisation, the EMEA (through CHMP) gets involved, and functions as an arbitrator. In that case, the opinion of the CHMP is transmitted to the European Commission. If minor or no objections are raised by the Member States, the authorisation is published in the Official Journal of the European Communities. The mutual recognition is compulsory for any 'non centralised' product sold in more than one Member State.

The national procedure

Market authorisation exclusively for one country can of course still be obtained through the medicine agency of that particular Member State. These medicine agencies (also called 'licensing agencies') also have the national responsibility of pharmacovigilance and classification of all authorised products irrespective of procedure. However, as soon as the manufacturer seeks market admission in another Member State, the mutual recognition procedure becomes compulsory. Through the Heads of Medicines Agencies (HMA), the various European national medicine authorities are in regular contact on issues of Community interest.

The criteria for the authorisation of pharmaceuticals in Europe are based on the EU-wide good clinical practice standards and include proven safety and efficacy as laid down in Directive 2001/20/EC (see below). Only a small beneficial effect needs to be demonstrated in order to fulfil the efficacy criteria and cost effectiveness is not included. This implies that a newly licensed pharmaceutical does not necessarily have higher therapeutic benefits. Cost effectiveness does not become an issue in most countries until the reimbursement decisions

[35] The concerned national medicines authorities responsible for licensing, classification and pharmacovigilance can be found at www.hma.eu.

for coverage under the SHI/NHS is made. The role of the authorisation procedure is mainly 'checking' whether the product works, whether it is safe and of good pharmacological quality. Directive 2003/94/EC of 8 October 2003 lays down the 'principles and guidelines' of good manufacturing practice of pharmaceuticals. Title IV and V of the Community Code cover further legal requirements for manufacturing, labelling and package leaflets.

4.1.2 Pharmacovigilance

After the pharmaceutical is approved, whether or not on the basis of the centralised, decentralised or national procedure, the pharmaceutical is subject to post-marketing surveillance, or pharmacovigilance. Pharmacovigilance can be seen as a continuation of the evaluation of the pharmaceutical. Although pharmacovigilance used to be a solely national matter, after the Thalidomide tragedy, Directives 65/65/EEC and Directive 75/319/EEC –now part of the Community code relating to medicinal products for human use– forced all actors to collect, collate and exchange adverse drug reactions (ADRs) within the European Economic Area. However, Directives are binding on Member States as to the results to be achieved and many of the regulatory requirements were already covered under existing national law. The UK, for example, had its 1968 Medicines Act. Consequently, many different systems with different reporting patterns were put in place or were already in place.

Furthermore, because of the new authorisation procedures, the approved medicine gets exposed to much larger populations simultaneously than under the pre-1995 European situation. These developments raised concern about the pharmacovigilance standards in Europe and better understanding of the various national systems was necessary before it could be used for pharmacovigilance assessment for the EU as a whole. Therefore, the Eudravigilance data processing network and management system was launched in December 2001. It has been developed according to internationally agreed standards. As a result, the EMEA implemented the electronic data exchange of Individual Case Safety Reports (ICSRs) of marketed medicinal products. The system enables the exchange of pharmacovigilance data between national medicine agencies, the EMEA and pharmaceutical industry.

Since 1 may 2004, Directive 2001/20/EC[36], the 'Clinical Trials Directive' is fully implemented. The directive aims to simplify and harmonise the administrative provisions governing clinical trials by establishing a clear, transparent procedure and creating conditions conducive to the effective co-ordination of such clinical trials in the European Community by the medicine agencies concerned. This means that from now on sponsors of clinical trials need to obtain a EUDRACT number from the new EUDRACT database in order to collect all relevant information about suspected serious unexpected adverse reactions (SUSARs). This information is then reported to all authorities concerned. Eudravigilance does not only cover the post authorisation phase, but also the pre-authorisation phase.

4.1.3 Distribution and classification of pharmaceuticals

When the pharmaceutical enters the national market, the pharmaceutical wholesalers are subject to national regulation, stemming from, again, the Community Code relating to medicinal products. The Code has a full title dedicated to wholesaling (Title VII) and integrates the 1992 Directive (92/25/EEC) on wholesale distribution. The Code includes the requirement for the possession of an authorisation before engaging in wholesale activity, forces the Member States to check on the authorisation holder and suspend or revoke the authorisation if authorisation conditions are not met. Some of these conditions that have to be ensured by the Member States for their respective authorisation holders are: adequate premises, qualified staff, precise recordkeeping, emergency plans for market-withdrawal of pharmaceuticals and being able to provide information that makes it possible to trace the distribution path of every medicinal product. Similar to the guidelines for good clinical and manufacturing practice, there is a guideline on Good Distribution (94/C 63/03[37]), which provides guidelines in accordance with the Community Code.

Pharmaceutical products can be dispensed by hospitals, community pharmacies, and depending on their classification and Member State, also by drug stores and supermarkets. The European pharmacy sector is a heavily regulated and controlled field. In a study of regulation of professional services in the EU, conducted for the Directorate General for Competition, Paterson et al. (2003) found that the pharmacists' profession is the field with the

[36] Directive 2001/20/EC of the European Parliament and the council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.
[37] Guidelines on Good Distribution Practice of Medicinal Products for Human Use (94/C 63/03)

most extensive, restrictive regulation of all the researched professions (accountants, lawyers, engineers and pharmacists). Pharmacies must be licensed under national regulation in all EU Member States. Depending on Member State, the agency responsible for this range from the French Départments and German Länder, the Health Inspectorate in the Netherlands, the medicine agency in Finland, the health department (Belgium, Denmark, Portugal), The Royal Pharmaceutical Society in the UK and the College of Pharmacists in Spain (Taylor et al., 2004a). In Sweden pharmaceutical products are sold through state monopoly, and only one state owned company is carrying out the services of pharmacies. Portugal, Austria, Belgium, Denmark, Finland, France, Italy, Spain, Greece and Luxembourg have quite extensive regulations, in which the number of pharmacies is restricted, for example through economic needs tests and pharmacies relative to population numbers. Ireland, Germany, the UK and the Netherlands do not have these kinds of restricting market entry regulation (Paterson et al. 2003). Except in Belgium, Ireland, the Netherlands, Sweden and the UK, only pharmacists or partnerships of pharmacists can own pharmacies. In the Netherlands, for example, interested (non-pharmacist) parties are allowed to employ pharmacists since 1999. This paved the way for pharmacies owned by supermarkets, chemists, insurers, industry et cetera.

Each Member State has its own medicines classification system, which is set up to ensure that the public benefits from the pharmaceutical while minimizing chances of inappropriate use and harm to the user. Classification is the responsibility of the Medicine Agency[38] (licensing authority) of the concerned Member State. In most of the European countries (e.g. UK, France) medicines are classified into three categories, namely: prescription only medicine (POM) also known as Rx, pharmacy-supervised sale (P) or general sales list (GSL). Some Member States use only two categories, which can be compared to POM and GSL.

POMs can only be supplied when recommended/endorsed by a medical practitioner and dispensed through a community or hospital pharmacist. The over-the-counter (OTC) market, medicines for sale without prescription, is made up from the P and GSL categories. The Member States show major distinctions between the P and GSL categories. In most countries, medicines in the P category can only be sold under the supervision of a pharmacist. On the other hand, both pharmacists and retail outlets, e.g. chemists or supermarkets, can sell pharmaceuticals from the GSL category. This is not necessarily the case in all countries, for example in Italy and France, the P and GSL categories are only available through a

[38] The concerned national medicines authorities responsible for licensing, classification and pharmacovigilance can be found at http://heads.medagencies.org/index.html

pharmacist, though GSL may be displayed in areas for customer self selection and advertised to the public (Bond et al. 2004). In the Netherlands, which until 2007 only knew the POM and GSL categories, a deregulation is adopted, that splits the OTC category in three (Staatsblad 2007). Apart from a P and GSL (all retail outlets) category, there is a third intermediate category that can only be sold by pharmacies and chemists (hence, comparable to the Italian and French interpretation of GSL).

The 'Classification Directive' (92/26/EEC[39]) –now under Community Code Title VI– came into effect in 1992 and harmonises (on a European level) the criteria that determine whether a product should be sold as an OTC or a POM. It is important to note, however, that these criteria are applied nationally, and therefore have considerably different outcomes across Member States as to which pharmaceutical will receive POM or OTC status. A Europe wide trend can be observed as the OTC market is expanding in terms of value, volume and range of products (Bond et al. 2004).

4.1.4 Advertising

Following Directive 92/28/EEC –now under Community Code Title VIII–, the public advertising of POMs is prohibited, whereas public advertising of OTCs is allowed in most cases[40]. Most Member States already had a similar distinction and rules in place. As a consequence of the inconsistencies between countries regarding the classification decision, there are differences between countries as for which pharmaceuticals advertising is allowed. Member States have their own regulatory frameworks in place as to what degree there are further controls on OTC pharmaceuticals. The objectives of these constraints are related to public safety and competition issues. A clear distinction has to be made between advertising and information to patients. In contrast to the European framework for pharmaceutical advertising, the issue of national information provisions did not lead to harmonisation between Member States. Although several Commission initiatives and repeated public debates focused on the need to address this lack of a Community framework on information to

[39] Directive 92/26/EEC, of 31 March 1992 concerning the classification for the supply of medicinal products for human use

[40] Until recently, EU legislation prohibited advertisements to the public for chronic insomnia, diabetes and other metabolic diseases, malignant diseases, serious infectious diseases including HIV-related diseases and tuberculosis and sexually transmitted diseases. These restrictions were removed with the pharmaceutical review.

patients, the legal situation has not changed fundamentally over the last 15 years (European Commission 2007).

4.2 NHS/SHI regulation with potential impact on entire national market

There is a considerable amount of national cost containment measures, which can have – depending on how they are applied– strong influence on the entire pharmaceutical market, i.e. outside the NHS/SHI (non-publicly covered medicines). As shown below, direct price controls and prescribing and dispensing measures can have consequences for the entire pharmaceutical market. A myriad of cost-containment measures have been taken during the 1990s, which were often copied from each other, even though reliable information about the successes and failures of measures adopted elsewhere was not gathered (Maynard and Bloor 2003; Guillén and Cabiedes 2003). There are quite some studies that tried to link price level with the regulatory framework– often with significant discrepancies. Some suggest prices are kept lower through a strict regulatory framework (Garattini et al. 1994; Johnsson 1994; Rovira and Darba 2001), while others suggest that in countries with less regulation, prices tended to be lower through competition (Reekie 1998; Danzon and Chao 2000). These discrepancies in findings reflect the different methodological approaches, including the range of products considered (particularly whether off-patent generics were included) and the period the data covered and method of calculating the indices (Mrazek and Mossialaos 2004). Furthermore, looking at total pharmaceutical spending (not just prices), there is information suggesting that the policies adopted in EU countries during the 1980s and 1990s have not been effective in controlling public pharmaceutical spending (Guillén and Cabiedes 2003).

All in all, it illustrates the difficulties Member States experience controlling their pharmaceutical expenditures and developing successful pharmaceutical cost containment policies. This Section seeks to provide an overview of the wide variety of pharmaceutical cost-containment regulation in place across the Member States. It does not seek, however, to provide an exhaustive and completely updated listing of measures as this is beyond the scope of the thesis and basically unfeasible. The goal of this thesis is to look at national policies and Member States in a general sense rather than dealing with these on a ‘country to country’ basis.

4.2.1 Direct price controls and profit controls

Price control measures aim to contain the rising public expenditures on pharmaceuticals, in other words the expenditures within the SHI/NHS system. However, these measures may have impact nation-wide, on the entire national pharmaceutical market, on all authorised medicines. This depends on the scope of the regulation in force: when it only affects reimbursed medicines, the cost containment effects are strictly limited to within the SHI/NHS.

With direct price controls, the government simply sets maximum prices for pharmaceuticals. How these prices are set varies from country to country. They may apply to all medicines, or to specific pharmaceutical groups, such as all reimbursed medicines, off-patent (generics) or only on-patent pharmaceuticals. At what level these prices are fixed, depends on several country specific factors, including budget limits, prescribing behaviour, patterns of utilisation and the importance of pharmaceutical industry to the national economy (Mrazek and Mossialos 2004). In most European countries pharmaceutical prices are controlled. The UK and Germany are the only EU15 countries in which in patent drugs can be freely priced at launch. In France, free pricing for medicinal products defined as 'innovative' was introduced in 2003. It does not come as a surprise that these three Member States hold the largest pharmaceutical industries in the EU. In the UK, however, prices are moderated indirectly through control of the profits obtained by pharmaceutical industry. The so-called Pharmaceutical Price Regulation Scheme (PPRS) regulates profits to a band of 17-21 per cent on historic capital, with 25 per cent variation on either side. If companies set their prices in such a way that profits are higher than the band, the pharmaceutical company has to reimburse the NHS, or reduce the profits. If profits were lower, the company can raise its prices. However, the scheme offer little incentives to be efficient, as such behaviour reduces cost, and raises the profits– which then have to be reimbursed to the NHS (Maynard and Bloor 1997).

Member States use different price setting schemes, of course reflecting their respective policy priorities. Prices are directly controlled through negotiations with industry (Austria, France, Italy, Portugal, Spain and more recently the Netherlands), fixed by national authorities through a list of factors, including discretionary criteria that are subjective, open to bias and could result in a lack of transparency (Mrazek and Mossialos 2004), or by a combination of both. Examples of such factors are price comparisons between similar products within a country or comparison with identical or comparable products in other countries, such as the

use of international comparisons (see table 13) of ex-manufacturers price (e.g. Belgium, Denmark, Netherlands, Italy, Portugal) or wholesale price (e.g. Finland, Ireland). The Netherlands, for example, uses the ex-manufacturer's price in their neighbouring countries as a maximum, but also tries to influence the prices of generics through yearly agreements (called 'covenants') with the generic industry, pharmacists and health insurers.

Table 13 Examples of price comparison measures in Europe

Member State	Price comparison
Belgium	Ex-manufacturer's price in France, Germany, Luxembourg and the Netherlands
Denmark	Average European ex-manufacturer's price excluding Greece, Portugal, Spain, and Luxembourg, but including Liechtenstein
Finland	Average EU wholesale price
Ireland	Average wholesale price of Denmark, France, Germany, the Netherlands and the UK
Italy	Weighted average ex-manufacturer's prices in EU (excluding Luxembourg and Denmark)
Netherlands	Average ex-manufacturer's price of Belgium, France, Germany and the UK
Portugal	Minimum ex-manufacturer's price of identical products in France, Italy and Spain

Source: Mrazek and Mossialos (2004)

Whether price controls are effective in reducing pharmaceutical expenditures is heavily debated. The introduction of stricter price controls is often accompanied with increasing expenditures (Mrazek and Mossialos 2004). That prices go down does not necessarily mean that expenditures automatically go down too: the volume component or the shift to other medicines can still make up for the lower price. An often observed effect is that pricing measures seem to work in the short term, but lose their effect on the longer term. Possible explanations are that industry is able to create 'escape valves' by increasing the sales of already commercialised products and/or obtaining more favourable prices via product differentiation through new trademarks (Guillén and Cabiedes 2003).

The 1989 European Transparency Directive forces Member States to adopt verifiable and transparent criteria in setting pharmaceutical prices and their inclusion in national health insurance systems. It does not regulate European wide price controls or profit caps, nor does it seek to harmonise rules of the various national reimbursement schemes. It does, however, set a 90-day limit for adopting a decision on the price. The Transparency Directive is the only European directive in force in the field of pricing.

4.2.2 Measures regulating prescribing and dispensing

Stimulating the use of generics

Generics are off patent drugs, are usually sold under their chemical name and are possibly manufactured by more producers than just one and consequently, are more price-competitive. As visible in table 14, there are various options to stimulate generic use that are aimed at the demand side of the pharmaceutical market[41], i.e. either directed towards the physician, who is responsible for the prescription, or towards the pharmacist, who is responsible for dispensing the pharmaceutical. The size of the generics market has grown in a number of Member States in the past few years and is expected to continue to grow in the near future. In countries that had promoting policies for generics (Germany, Denmark, Netherlands and the UK), the generic market (as a percentage of total prescriptions) is notably bigger than in countries that did not have such policies in place (e.g. France, Spain) (Mrazek and Frank 2004). This is illustrated by Simoens and De Coster (2006), who had access to IMS Health and EGA data and distinguished two groups of countries in terms of share of generic medicines by volume in 2004. The first group is made up of countries with a 'mature' generic market, in which the volume of generics exceed 40% market share, e.g. Denmark, Germany, Netherlands, Poland and the UK. The second group consists of countries with developing generic markets, in which generics make up less than 20% of market share, e.g. Austria, Belgium, France, Italy, Portugal and Spain. Their study finds that there is no single approach towards developing a generic medicines market, but countries that have promoted generic medicines in the past 10 to 15 years –as a consequence– have more mature generic markets than countries that have only recently implemented such policies.

For example, the Netherlands, which has seen the greatest drug substitution (Guillén and Cabiedes 2003), the Dutch government, in alliance with pharmacists and medical organisations, tries to stimulate a more rational prescribing behaviour through the use of 'electronic prescribing' programs in which a computer helps to give suggestions for a generic substitute (EVS, Electronisch Voorschrijf Systeem).

[41] There are also supply side policies that can stimulate the use of generics, e.g. reference pricing schemes.

Table 14 Incentives to promote generics in the EU

Targeted on	Method	Country
Physician	Generic name prescribing encouraged or required	Finland, France, Germany, Ireland, Italy, Luxemburg, Netherlands, Portugal, Spain (some regions), UK
	Prescribing budgets	Germany, Italy, Ireland, UK
	Pay agreement linked to prescribing	Spain (local schemes)
	Dissemination of information to promote generics	Belgium, Italy, Ireland, Portugal, UK
	Prescribing guidelines	France, Netherlands, Portugal, UK
	Monitoring prescribing	Austria, Belgium, Denmark, Luxembourg, Netherlands, UK
Pharmacist	Generic substitution	Denmark, Finland, France, Norway, Spain
	Multi sources product selection only if prescription written using the generic name	Italy, Germany, Luxembourg, Portugal, Netherlands, Sweden, UK
	Margins that encourage generic dispensing	France, Netherlands, Norway, Spain, UK
	Dispensing budgets	Denmark

Source: Mrazek and Mossialos (2004)

Rationalisation of prescribing

The promotion of generics makes up a great part of most countries' aim to *rationalise prescribing behaviour*, but these attempts do not constrain themselves to generics. Some of the methods mentioned in table 14 (e.g. guidelines, information campaigns, monitoring), can also be used to promote a more reluctant prescribing behaviour, to give advice on drugs and optimal length of treatment for each condition, and provide support in making a more cost aware decision– whether or not with the use of a computerised decision support system. All European countries apply prescribing guidelines to some extent and a trend is visible, but not all of them apply them in a systematic and generalised way (Guillén and Cabiedes 2003).

How guidelines are designed, using which criteria differs from country to country. In general, they are not regarded as a substitute for a physicians' clinical judgement. In the UK, guidelines are the responsibility of the National Institute of Clinical Excellence (NICE). NICE guidelines include cost effectiveness insights and are targeted at both physicians and patients. France uses guidelines, drafted by experts and professionals, which are framed as statements about what should not be prescribed –the *références médicales opposables*. In theory, lack of compliance generates a fine related to harm, cost and the extent of deviance, although most practitioners are not even aware of these rules, and their administration is so complex that

they have been little used as control devices. In Germany, prescribing guidelines were introduced in 1995 and function in close relation with the 'negative list'. However, these guidelines were not subject of systematic analysis, so the effects on quality and spending are unclear (Maynard and Bloor 2003).

Remuneration of community pharmacies

The most common way in Europe to remunerate community pharmacies is through a percentage of prices (e.g. Austria, Belgium, Finland, Greece, Italy, Portugal and Spain). This can make it attractive for community pharmacies in these countries to supply more expensive medicines– from a cost-containment point of view an undesired situation. Key in controlling pharmacy reimbursing policies is attempting to take away the incentive to sell more and more expensive pharmaceuticals. It has been shown that this can be achieved by taking away the link between pharmacists' remuneration and the price or quantity of drugs. Different schemes are in place. Some countries have margin-ceilings (Spain), use margins that diminish as prices rise (e.g. France, Germany until 2003) or have fixed amounts per dispensation, regardless of drug price (UK, Sweden, Ireland and the Netherlands). A combination of a small price percentage and a dispensing fee is used in Germany. Since 2004, the pharmacy is remunerated 3% of the price of the pharmaceutical and a fixed dispensing fee of €8.10. In Denmark, the Ministry of Health offers a yearly amount to compensate community pharmacies that have low levels of dispensation (Guillén and Cabiedes 2003). However, the question remains why there are still so many countries with a system that contains an incentive to sell more expensive medicines.

4.3 NHS/SHI pharmaceutical regulation

The regulation in this Section is strictly within a Member State's National Health Service (NHS) or Social Health Insurance (SHI) scheme and generally falls within the Member States' sphere of competence.

4.3.1 Measures regulating the reimbursement of pharmaceuticals

Positive list and negative list ('selective listing')

Most European countries appear to operate a so called 'positive list' or are moving towards a positive list (McGuire et al. 2004). The criteria and schemes, through which pharmaceutical products are approved for reimbursement and put on a positive list, vary by country. The Transparency Directive 89/105/EEC, however, specifies a 90-day limit for taking a reimbursement decision. In most countries, therapeutic benefit is the main criterion, but cost effectiveness compared to products already reimbursed is growing in popularity. Germany is the main exception as a country that still operates a negative list, which lists pharmaceuticals excluded from reimbursement. Newly authorised pharmaceuticals are automatically reimbursed, which makes the Transparency Directive's 90-day limits effectively superfluous. Long existing plans to shift to a positive list have so far failed. The UK operates a selective list, which formally still exists as negative list, in which since 1999, advice on cost effectiveness criteria is given through the National Institute of Clinical Excellence (NICE, see below). In France, pharmaceuticals are –since 1999– reimbursed according to their medical effectiveness (Service Médical Rendu, SMR). A reform in 2003 followed the advice of the 'Commission de Transparence' (part of the 'Haute Autorité de Santé') and reduced reimbursement rates for 617 drugs. Another 84 drugs were de-listed in the summer of 2003 (Busse and Schlette 2004).

Economic evaluation/ post-licensing evaluation

A manufacturer has to provide evidence of the quality, safety and efficacy of their product in order to get their product authorised. However, these three 'hurdles' are no longer sufficient to ensure a positive reimbursement decision. It is for this reason that throughout the EU and other industrialised nations, there is an increasing interest for complementing pharmaceutical reimbursement procedures with a 'fourth hurdle' of demonstrable cost-effectiveness. A couple of factors seem relevant in regard to the rise in use of cost-effectiveness studies for pharmaceutical prices or reimbursement. Apart from the more obvious reasons such as rapidly growing pharmaceutical expenditures, the increasing number of prescribed items and growing awareness about failing national regulations, a propensity towards prescribing newly introduced drugs is commonly noticed throughout Europe. New innovative drugs tend to have higher average prices than existing products (McGuire et al. 2004), making it even more urgent to examine their relative cost-effectiveness.

A number of EU states are developing or already using 'post-licensing evaluation' systems that include the use of economic evidence in comparative drug evaluation when making reimbursement decisions. Pioneer in the EU is the UK, where since 1999 the National Institute of Clinical Effectiveness (NICE) is advising the NHS, not only on clinical effectiveness, but also on cost effectiveness of new products. NICE requires companies to hand in evidence of the costs and effects of new products. Recommendations are generally for subgroups of patients and are guided by cost-effectiveness and cost-utility analysis. Whereas NICE also provides guidelines to physicians and patients (see rationalisation of prescribing), in most European countries health economic evaluation is used as an additional requirement in the reimbursement decision-making process. These countries include Belgium, Finland, Norway, Portugal, Italy, the UK, Sweden, Spain and the Netherlands (McGuire et al. 2004; Taylor et al. 2004b). Other countries, such as France, Finland, Norway and Denmark, include cost-effectiveness as supporting evidence for reimbursement or pricing (McGuire et al. 2004). In 2004, Germany established the Institute for Quality and Efficiency in Health Care (IQWiG), which in the future may have an evaluation function (Zentner et al. 2005). Hungary has become one of the first Eastern European countries to signal the introduction of economic evidence as a formal requirement (Taylor et al. 2004b).

Co-payments (cost- sharing)

The majority of European countries use co-payments, in which the consumer makes a contribution towards the financing of pharmaceuticals ('cost sharing'). During the 1980s and 1990s –with some exceptions– cost sharing increased, rising the level of private expenditure on drugs. It aims to increase efficiency by reducing excessive demand and containing overall health costs. In a study prepared for the European Commission DG Employment and Social Affairs, Thomson et al. (2003) distinguish three different forms of cost sharing in Europe. First, *co-insurance*, the most common form, requires the patient to be liable for some percentage of the total cost of the pharmaceutical (Belgium, Denmark France, Greece, Luxembourg, Portugal and Spain); secondly, *flat-rate payments*, in which the patient pays a fixed fee per item or prescription (Austria and the UK); and thirdly, *deductibles,* which oblige the patient to bear the initial expense up to a specified amount (e.g. Denmark, Ireland, Sweden). Some countries may also use combinations of these three. Finland for example, uses combinations of deductibles and co-insurance. Some countries also opt for exemptions or reduced rates for vulnerable population groups. These exemptions and reductions are

commonly based on clinical condition, level of income, age or type of drugs. Examples of such groups are: low income groups (e.g. Austria, Belgium, and Germany), the elderly (e.g. Belgium, Ireland, and Spain), children (e.g. Germany, UK), people with chronic illnesses (Portugal), and people with life threatening illnesses (Belgium). Also combinations exist, such as older people with low income (Greece) (Thomson et al. 2003; 2004).

However, its effectiveness as a policy tool is heavily debated in academic circles. In general, co-payments have had very limited success in controlling pharmaceutical expenditures in EU Member States. Also, their deterrent effect may apply to both unnecessary treatments as highly effective ones (Guillén and Cabiedes 2003). Consequently, it is a sensitive social issue, evoking political debate and patient group and media attention about its feasibility and equity implications.

Prescribing Budgets

In some Member States, doctors are allocated prescription budgets or a practice budget, including prescription medicines. Examples of these countries are the UK, Ireland, Germany, France and Denmark. Various studies into the effects of budget holding in the UK (GP fundholding) showed only short-term effects on drug spending (e.g. Bradlow and Coulter 1993; Stewart-Brown et al. 1995; Walley et al. 2000).

In the UK, primary care trusts (PCTs) were introduced in 1999, replacing the individual GP-fundholding system. The PCT is responsible for purchasing a wide range of services, including prescribing. The PCT can only purchase collectively, and benefits through savings are collective too. The scheme hopes to use peer pressure to develop a sense of corporate affinity among GPs to control overall prescribing. However, both the reluctant and the generous GP may benefit from cost aware behaviour. This reduces the incentive and might reduce support of the enthusiasm for prescribing (Walley and Mossialos 2004).

In Germany, cash-limited prescribing budgets were set up collectively from their start in 1993. In its 9-year history –the scheme was abolished in 2001– the scheme underwent some changes and always evoked discussions about its cost containment and quality of prescribing effects.

4.3.2 Reference pricing schemes

A reference pricing scheme sets limits for pharmaceuticals assigned to the same group of therapeutic substitutes. If the consumer wishes a more expensive drug, or the doctor prescribes a more expensive drug, the consumer has to bear the difference in price. Some authors view reference pricing as a form of cost sharing, albeit a more voluntary one as reference pricing schemes often provide co-payment-free alternatives. On the demand side, the scheme hopes to raise awareness of the prescribed drug's price and should stimulate both patient and doctor to opt for a drug listed at the reference price or below. On the supply side, it hopes to stimulate manufacturers to lower their prices to the reference price. The scheme may be broadly or narrowly defined; including all generics and some patented drugs (e.g. Netherlands) or just a small selection of generics (e.g. Spain). Furthermore, states use different systems to establish the reference price (table 15)

Table 15 Comparative definitions of reference price in selected EU schemes

Country	Introduced	Definition of reference price
Germany	1989	Reference price should not surpass the highest price in the bottom third of the price range for drugs containing the same active substance and having comparable efficacy
Netherlands	1991	Average price of drugs with similar (pharmaco-) therapeutic effects
Denmark	1996	Lowest priced generic equivalent available on the market
Spain	2000	Arithmetic mean of the three lowest cost-per-treatment-day grouped by formulation and calculated by DDD
Belgium	2001	Equal to a price that is 26 per cent lower than the price of the original brand for generic equivalent products
Italy	2001	Lowest priced generic equivalent available on the market
Portugal	2003	Lowest priced generic equivalent available on the market

Sources: Mrazek and Mossialos (2004); Simoens and De Coster (2006)

Although reference pricing seems to have a positive short-term effect on pharmaceutical spending (Guillén and Cabiedes 2003), the effects do not result in important long-term savings (Lopez-Casanovas and Puig-Jumoy 2000). One explanation is that increase in volume and price of drugs outside the reference price system in general nullified any reductions in pharmaceutical spending from the scheme (Mrazek and Mossialos 2004). In the Netherlands for example, many manufacturers raised their prices towards the price limit and price increases up to 500% were observed (Snier 1995). Furthermore, manufacturers and

wholesalers have been paying bonuses and have been giving discounts to community pharmacies where their respective products were dispensed, which 'undermines' the system. Also, it is said to hinder payers in effectively negotiating medicine prices, a task insurers have in the new governments' plans to make the insurers a 'countervailing power' on the demand side of the Dutch pharmaceutical market. Therefore, the failure of reference pricing in the Netherlands is widely acknowledged and its abolishment is due. However, in contrast with the Dutch experience, France is implementing a reference pricing system without the accompanying controls the Dutch experience indicates is necessary (McGuire et al. 2004). Also Spain has altered its reference pricing system in an attempt to curb the pharmaceutical expenditures, which mounted to +11% in 2003 (Busse and Schlette 2004).

4.4 Pharmaceutical policy in the new Member States (EU12)

Most of the new Member States of the European Union (the EU12) [42] cannot so easily be compared to the EU15 countries. The reform process for the pharmaceutical sector in the Eastern European new Member States[43] began when communist ideology gave way to democracy and market liberalisation: from a supply based, centralised system –often characterised by shortages and inadequate supplies– towards a system with a liberalised pharmaceutical sector, with a flood of new imported pharmaceuticals–often against unaffordable prices. The changes meant above all privatisation of state industry and the distribution network.

A reform of regulation after western European standards has been driven by the desire of EU access and included measures such as market authorisation, patent legislation, manufacturing standards, licensing requirements as well as drug pricing and reimbursement. These developments drove the EU12 countries to install in 10 years what most EU15 countries have been working on the last 40 years. To facilitate this process, the Pan-European Regulatory Forum (PERF) was created for both regulators in the EU15 and the candidate countries (initially the 10 countries that joined 2004) to identify practical arrangements for implementing the EU regulatory framework for pharmaceuticals in anticipation of the 'big

[42] The EU12 are: Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia, Slovenia (all joined May 2004), Bulgaria and Romania (joined January 2008).
[43] Cyprus and Malta are the exception being southern European democratic countries, with no communist history.

bang' enlargement of 2004. It went through three stages of development between 1999 and 2004, known as PERF I, PERF II, and PERF III, and sought to address topics such as, quality, safety and efficacy in a European context.

One important consequence of the massive shift to imported drugs was the escalation of pharmaceutical expenditures. For example, in Slovenia, the average cost of drugs increased by 70 per cent between 1990 and 1999 (Albreht et al. 2002). Also, because of the new imports, the list of available drugs skyrocketed in Hungary, from 1300 drugs in 1990 to 10577 in 2002. The huge increases in pharmaceutical costs raised awareness for the need for cost containment programs. The EU10 countries adopted approaches widely used in the EU15 (Mrazek et al. 2004) such as selective listing, with full, partial or no reimbursement (Czech Republic, Poland, Slovakia); partial coverage according to disease severity (Hungary, Latvia, Slovenia) or type of drug (Poland).

Prices have been regulated by a number of mechanisms including price negotiation (Hungary, Poland, Latvia, Lithuania), international price comparisons (Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Slovenia), setting the ex manufacturer's price (Slovakia, Lithuania), reference pricing (Czech Republic, Estonia, Hungary, Lithuania, Poland, Slovakia) and economic evaluation (Estonia, Latvia, Lithuania). As in Western Europe, the approaches are multiple, ever changing, and complex (Mrazek et al. 2004). The countries have predominantly focused on reimbursement and pricing in favour of the measures affecting prescribing and dispensing. With this, they follow the patterns observed in Western Europe.

PART II: SCENARIOS

5 METHODOLOGY

This thesis aims to shed light on possible directions for the future and whether this future will bring more European influence or a strengthened national influence. In this Part II of the thesis, which consists of Chapter 5 and 6, an answer to these questions is given by developing and describing three scenarios for European pharmaceutical policy. In the analysis, Part III of the thesis, these scenarios will be confronted with the findings from Part I, the literature review. This Chapter describes the chosen methodology for framing the scenarios. In order to make assumptions on the course of the issues and key variable, and to be able to frame the scenarios, the Delphi-technique was selected as a tool. Therefore, Section one discusses the Delphi method and why this methodology was chosen over other methods. In the second Section the Delphi method will be applied to the particularities of the pharmaceutical market leading to European Pharmaceutical policy questionnaire. In Section three the process of selecting experts is elaborated upon, before Section four describes the conduct of the chosen Delphi design.

5.1. The Delphi Method

The Delphi technique is a procedure aimed at obtaining a reliable consensus of opinion from a group of experts through a series of questionnaires interspersed with controlled feedback (Garret 1999). In this process, the range of the answers will converge towards the 'correct' and final answer, which is provided by the median scores. The decision to work with the Delphi method was made because it brings multiple experts to this thesis, giving it more scientific value compared to a situation in which the scenarios just stem from one person's ideas, imagination and perception of the studied material. The main alternative, having expert meetings, for example using the Nominal Group Technique (NGT), a method similar to Delphi except that it allows some group discussion though final judgements are made in isolation (Van de Ven and Delbecq 1971), was unfeasible. Experts come from all corners of the European Union and scheduling a meeting with all of them would be infeasible from a cost perspective, in particular in the context of the limited funding of this thesis. Even assuming that experts could (and were willing) to participate, there would be room to influence each other leading to a possible bias. In addition, traditional group meetings are an inefficient and ineffective method for making forecasts and decisions (Green et al. 2007). A

systematic review undertaken by Rowe and Wright (1999) looked at several empirical studies that analyse the Delphi technique as a forecasting tool. They found that Delphi groups outperform statistical groups (by 12 studies to two with two 'ties') and standard interaction groups (by five studies to one with two 'ties'). Furthermore, the Delphi method is an established procedure that has been extensively reviewed in various studies (e.g. Linstone and Turoff 1975; Lock 1987; Stewart; Rowe et al. 1991; Rowe and Wright 1999) and can bring some quantification to the scenarios.

The Delphi Method was developed by Helmer, Dalkey and Gordon at the Rand Corporation at the beginning of the cold war to forecast the impact of technology on warfare. Over the years, new applications have been developed such as the policy Delphi (1970s), which seeks to generate the strongest opposing views on the resolution of a major policy issue and does not have consensus as its main objective (Turoff 1970); the Argument Delphi, which focuses on ongoing discussion and finding relevant arguments rather than focusing on the output (Kuusi 1999); the disaggregative policy Delphi which seeks to cluster quantitative expert or interest group responses into similar groups (Tapio 2002); and the wideband Delphi which involves more interaction and communication between experts. As visible in Garret's definition (1999) the key elements of the Delphi technique are the following:

1. Structuring the flow of information: the experts' contributions are collected in the form of answers to questionnaires and possibly their comments to these answers and no discussion among experts takes place. The panel director then processes the information and filters out irrelevant content. This avoids face-to-face panel discussions on differences in opinion which may lead to biased outcomes.
2. Providing feedback to the participants: the answers are sent back to the experts, who are then asked to take notice of all the comment (answers). After this, they can reconsider and revise their original answer. The method prevents the participants from adhering to previously stated opinions and/or conforming to a group leader. They then complete another questionnaire which is sent back to the coordinator. This can take up several rounds until a consensus is reached. It is also possible, however, that no consensus is reached but that respondents divide themselves in two or more groups. Some Delphi designs have this as a goal, e.g. the aforementioned (disaggregative) policy Delphi.

3. All participants maintain anonymity[44]: the identities are not revealed even after the completion of the final round and report. This aims to prevent participants from dominating others using their authority or personality, to free them from their personal biases, to minimise undesired biasing effects such as the 'halo effect'[45], to allow them to freely express their opinions, to encourage open critique and admitting errors by revising earlier judgments without losing face. Moreover, the results can not be ascribed to the expert by name and no responsibility has to be assumed.

For future studies, a Delphi design is often used to seek expert opinions on purpose, scope, key variables, actors, assumption sets, scenarios, strategies and tactics. The expert opinions are usually expressed through the assignment of weight (e.g. judging by probability, ranking by value) or the expression of choice from several possibilities rather than written answers to questions. A Delphi can therefore be used both for future research designs that are objective and exploratory and designs that are subjective and normative (Garret 1999).

5.2 The European pharmaceutical policy questionnaire

The aim of this Delphi questionnaire is to reach consensus among a group of selected experts on whether regulation in the European pharmaceuticals market will take a predominantly European or national course over the next twenty years. In the 'European policy' questionnaire, which was specifically designed for this thesis, experts were asked on key issues of pharmaceutical policy in Europe, how they estimate the current situation (the Delphi was conducted in 2006) and what they expect the situation to be in 2010, 2015 and 2025. The ten issues have been selected from the review (Part I of this thesis) and cover the whole range of regulation on all levels of the European pharmaceutical market, including: authorisation, pharmacovigilance, classification, distribution, advertising, pricing, dispensing, prescribing, post-licensing evaluation and reimbursement. The key variable for these issues ranged from 'fully national' to 'fully European'. As an additional dimension an extra category was added, asking for the experts' opinion on these issues.

[44] More novel Delphi applications may not guarantee full anonymity, such as the wideband Delphi.
[45] Halo Effect: generalisation from the perception of one outstanding personality trait to an overly favourable evaluation of the whole personality (Merriam Webster Online).

In order to achieve a high response rate, a very simple and short design with closed answer categories was preferred and constructed. Two rounds were expected to be enough to provide a picture of the overall trend as expected by the respondents. After a preliminary test round (see appendix A) –sent to a limited group of a European network the department participates in– to check whether the questionnaire, format (tables) and application were clear, the questionnaire was altered on two points. Since the response rate was rather disappointing, it was decided to shorten the introduction and to put the 'expert questions' Section (see below) at the end of the questionnaire so it would not immediately 'discourage' the respondents.

Some key features of the final first round design (see appendix B) are:

- The introduction emphasises that filling out the questionnaire should not take more than a couple of minutes. It also gives a deadline and asks to forward the mail.
- The questionnaire starts off with 'category of respondent'. The categories correspond with all the actors of the pharmaceutical market as displayed in the literature research of the thesis.
- The questionnaire includes a category on how the expert values the current situation, also to see whether there was unacceptable divergence in their estimation.
- The key variable ranges from 'fully national' to 'fully European'. This was combined with closed answer categories. On the question: 'Will the following issues predominantly be *regulated* and *implemented* at a European level or at a national level?' Respondents were asked to use a 5 categories Likert Scale: fully national (1), predominantly national (2), even or 50/50 (3), predominantly European (4), fully European (5).
- A list of expert questions was included in the questionnaire in order to possibly weigh the results and to check whether the right expertise was at hand. Also on this question, three answering categories (1=fully, 2=average, 3=not at all) were provided. They consist of two general questions, i.e. 'Would you consider yourself an expert in the field of European pharmaceutical policy, both on the European and national level?' and 'Are you familiar with the current state of the European pharmaceutical market, including its actors and recent developments?' but also two more specific questions, i.e. 'Are you familiar with European Law with regard to European health care, in particular the European Commission's public health competences (as laid down in e.g. article 152)?' and 'Are you familiar with European case law, especially Kohll/Decker, Smits-Geraets/Peerbooms and Vanbraekel and its possible consequences?'. The two

latter questions were included as European (Case) law was indicated in the literature research (Part I) as having a potential effect which could alter the future course of the European pharmaceutical market.

- The questionnaire contains an optional comments section.

5.3 Expert selection

Different sources supplied the 'experts' for the Delphi-questionnaire on European pharmaceutical policy. The questionnaire demands a very broad expertise on national and European pharmaceutical policy and knowledge of all the issues, ranging from authorisation to reimbursement. Recruiting good respondents, i.e. their e-mail addresses, in order to e-mail them, was done from the following sources:

- All the authors referred to in the literature research, and authors referred to in some standard works on European pharmaceutical policy were looked up in the internet, and where possible their e-mail address were noted down.
- The membership directory of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) was consulted. The directory contains the e-mails of the members.
- Various organisations (e.g. NGOs, companies) and interest groups, mentioned in the literature research, were mapped out by looking up their websites. Sometimes only an e-mail address for general information was found and used, sometimes personal e-mail addresses.
- Using the above mentioned sources clearly has an under representation of respondents with a pharmaceutical industry background as a result. E-mail addresses of experts working for pharmaceutical industry are hard to get through the internet. Therefore, all available business cards at the Department of Health Care Management of the TU Berlin were hand-searched for usable addressees.

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After perusing the sources and selecting the addressees, around 200 (alleged) experts were approached from all actors in the European pharmaceutical market. However, academics make up for the largest group of addressees and, consequently, respondents. When human judgement is required the key issue is how to best use and elicit expert opinion in forecasting situations.

5.4 Conduct of the Delphi-questionnaire

The conduct of the questionnaire has the aim to achieve the highest possible response rate. Therefore the questionnaire has the following features:

- The questionnaire was sent by e-mail. In this way, more people could be reached, also because respondents were invited to forward the questionnaire to colleagues. It is therefore significant to mention that in some cases this worked out very well and addressees forwarded the message to colleagues within and outside their institution of affiliation. Through this, the questionnaire even 'penetrated' institutions that could not be approached due to lack of e-mails open to the public.
- Another positive characteristic of using e-mail is that it is fast, easy and cheap. This not only holds true for the sender, but more importantly, for the respondents as well.
- The subject header of the email contains –apart from 'sender' TU Berlin– the words '(short!) Delphi questionnaire' and the date of the deadline (also see appendix B and C).
- The questionnaire was sent by e-mail and opens in the message window, i.e. not in an attachment. The reader is directly confronted with the questionnaire and sees that it is short, which aims to excite curiosity and a spontaneous reply. It was for this reason that it was decided against only using attachments that could be filled out and sent back, or using an interactive web-based design following a link, after which the respondents fill out their questionnaire online. Filling out the questionnaire online may be an elegant way to conduct a questionnaire and has some advantages regarding the processing of the evoked data, but in the end the immediate visibility of the questionnaire through the e-mail option preponderated. Furthermore, widely used HTML supporting e-mail programs have no difficulties displaying figures or tables, which make attachments (mostly) unnecessary.
- After receiving the e-mail and reading it, respondents were asked to reply to the e-mail, and fill out the questionnaire in the new reply e-mail. Although most e-mail programs support HTML-codes and respondents should have had no problems using this procedure, an attachment with the same contents as the e-mail was sent along as a backup. It later turned out that some respondents preferred using the attachment, maybe also because some of them encountered problems with their (non HTML

supporting) e-mail programs. After ten days, shortly before the expiring date of the original deadline, a 'reminder' message with an extended deadline (by ten days) was sent, containing the whole questionnaire and attachment anew so that the respondent did not have to look for the original e-mail.

- As mentioned earlier, the expert-questions were placed at the end of the questionnaire in order not to 'discourage' the respondent beforehand.
- In Round 2, only the addressees whose results were received and used in Round 2 were approached, i.e. no new addressees were added. It is evident that the respondents did not have to answer the 'category of respondent' and 'expert questions' sections anew. The results of the Round 1 'category of respondent' question were incorporated in the Round 2 questionnaire.

Anonymity

To ensure the full anonymity of the addressees' names (not only their results), the selected e-mail addresses were inserted in the 'blind copy' field (Bcc) of the e-mail and then sent simultaneously. Using this procedure, the addressees cannot see that other addressees are approached at the same time with the same email. In this way one does not have to send 200 individual emails.

6 RESULTS

After sending the e-mail with the questionnaire, a steady flow of responses started coming in with small peaks directly after sending the message and after sending the reminder. The first round yielded 41 usable filled-out Delphi questionnaires. Some respondents' answers were not used due to illegibility and/or insufficient expertise. The processed results were then anonymously incorporated in a new questionnaire (see appendix C) and sent again according to (almost) the same protocol as described under 'conduct of the questionnaire'. Of the 41 respondents in round one, 27 replied, which corresponds to a response rate of 66%.

The respondents come from various backgrounds (see table 16), the biggest groups are the academics, 'other' (e.g. consultants, WHO) and the pharmaceutical industry. Two explanations for this unevenly spread result are that (1) mostly academics and pharmaceutical industry made up the initial mailing list and (2) most actors lack broad knowledge about other layers of the European pharmaceutical market (e.g. a pharmacist might not know about current developments in authorisation or European law) which could have prevented them from responding.

Table 16 Category of respondents

	R1	**R2**		**R1**	**R2**
Pharmaceutical Industry (R&D)	7	5	National government / regulator	3	2
Pharmaceutical Industry (generic)			European Union	1	
Wholesaler	1	1	Academic	20	14
Pharmacist			Consumer organisation		
Insurer/payer (NHS, Sickness F.)	1	1	Other	8	4

R1=Round 1, R2=Round 2

In this Chapter, the scenarios for future pharmaceutical policy will be filled in. First, the results of the Delphi questionnaire will be discussed (Section one). These results were then used as building stones to fill in a 'most likely', 'Expert Scenario', which was then contrasted with a more 'optimistic' ('pro-European') and a more 'pessimistic' ('anti-European/national') scenario. The scenarios can be found in Section 2 of this Chapter.

6.1 Discussion of results of Delphi questionnaire

One could say that the median scores of the questionnaire show an extrapolation of current trends. The answers on the question 'Will the following issues predominantly be regulated and implemented at a European level or at a national level?' (see table 17) can be divided into two main groups.

In the *first group*, the experts foresee a further Europeanisation in the area of the European pharmaceutical market where the European Union and national governments share the competence. Europe has the most competence and European law has the largest (potential) influence. Authorisation, pharmacovigilance, classification, distribution and advertising show a steady and gradual trend towards European regulation.

The *second group* covers those sectors of the European pharmaceutical sector that overlap with the Member States' national health systems. Hence, those parts where supposedly the competence of the Member State prevails stipulating from Article 152 of the TEC. Therefore, pricing, dispensing, prescribing and reimbursement remain predominantly a national competence and just a slight change towards European influence is expected.

However, one major exception applies. Post-licensing evaluation, i.e. the use of comparative benefit and cost effectiveness studies in taking reimbursement decisions, which takes place 'within' the national health systems as a competence of the Member States, is not expected to remain a solely national matter but is expected to develop into a field of evenly spread responsibility.

The following results attract particular attention: First, although the respondents' answers show convergence in the second round, not for all issues a consensus is achieved, but a trend is visible. Second, in the second round 66% of the first round respondents filled out the questionnaire anew. It is a legitimate question to see whether those 66% showed convergence compared to their first round. However, the answers of the 34% that did not respond the second round were visible and influenced the 66% that responded so they have to be included. Third, interestingly, some very different views exist as to how the 'today' (2006) situation should be interpreted. Particularly advertising –and to a lesser extent classification– shows widely diverging views. Although 41% seem to think in the first round that advertising is a

fully national field, the remainder thinks it is predominantly national (19%) evenly spread (14%), predominantly European (22%) and even fully European (3%, i.e. 1 respondent, a clear outlier). This is a remarkable score bearing in mind the fact that since 1992 an advertising Directive exists (now integrated in the Community Code) which prohibits direct to consumer advertising of prescription drugs. An explanation for this spread could be the fact that European countries had similar policies in place even before the 1992 EC involvement regarding advertising and classification. This may affect the visibility and people's awareness of European involvement. The second round still shows disagreement and even more people now view advertising (54%) and classification (58%) as a fully national field. These scores are less convincing than on other issues, where consensus up to 90%, even 100% exists.

Table 17 Delphi questionnaire results

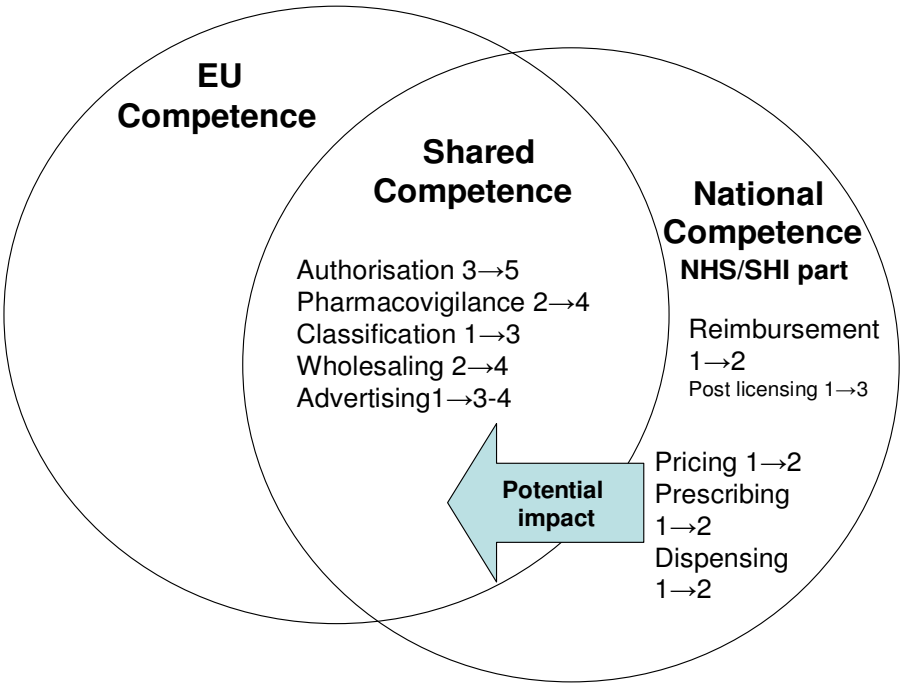
			EXPECTATION							
Issue	**2006**		**2010**		**2015**		**2025**		**Opinion**	
	Rnd1 (%)	**Rnd2 (%)**	**Rnd1 (%)**	**Rnd2 (%)**	**Rnd1 (%)**	**Rnd2 (%)**	**Rnd1 (%)**	**Rnd2 (%)**	**Rnd1 (%)**	**Rnd2 (%)**
1. Market Authorisation (Licensing)	1: 08		1:		1:		1:		1:	
	2: 23	31	2: 10		2:		2:		2:	
	3: 45	58	3: 45	73	3: 20	12	3: 05	04	3: 09	04
	4: 25	12	4: 38	20	4: 50	73	4: 45	30	4: 25	48
	5:		5: 08	08	5: 30	15	5: 50	67	5: 66	48
	n=40	n=26	n=40	n=26	n=40	n=26	n=40	n=27	n=32	n=25
2. Pharmaco-vigilance (post marketing surveillance)	1: 18	08	1: 08		1: 05		1: 05		1:	
	2: 49	65	2: 15	23	2: 05	08	2: 03	04	2: 06	
	3: 28	27	3: 51	58	3: 33	35	3: 23	11	3: 22	12
	4: 05		4: 23	15	4: 44	50	4: 44	59	4: 25	40
	5:		5: 03	04	5: 13	08	5: 26	26	5: 47	48
	n=39	n=26	n=39	n=26	n=39	n=26	n=39	n=27	n=32	n=25
3. Classification: Rx (Prescription only), OTC	1: 38	58	1: 18	20	1: 08	08	1: 03	04	1: 10	08
	2: 38	27	2: 38	58	2: 21	31	2: 21	22	2: 13	17
	3: 15	12	3: 23	15	3: 31	46	3: 23	37	3: 10	13
	4: 05	04	4: 15	04	4: 26	12	4: 28	22	4: 32	38
	5: 03		5: 05	04	5: 15	04	5: 26	15	5: 34	25
	n=39	n=26	n=39	n=26	n=39	n=26	n=39	n=27	n=31	n=24
4. Distribution (wholesaling)	1: 41	31	1: 15	12	1: 03	04	1: 03		1: 03	
	2: 46	62	2: 38	58	2: 36	31	2: 26	22	2: 19	17
	3: 08	08	3: 33	23	3: 33	50	3: 31	29	3: 35	33
	4: 05		4: 13	04	4: 26	12	4: 26	41	4: 23	38
	5:		5:	04	5: 03	04	5: 15	07	5: 19	13
	n=39	n=26	n=39	n=26	n=39	n=26	n=39	n=27	n=31	n=24
5. Advertising: e.g. direct to consumer advertising	1: 41	54	1: 16	20	1: 05	08	1: 03	08	1: 13	13
	2: 19	15	2: 34	36	2: 18	32	2: 16	15	2: 17	30
	3: 14	12	3: 18	12	3: 29	28	3: 24	31	3: 23	09
	4: 22	15	4: 26	28	4: 26	20	4: 29	27	4: 13	17
	5: 03	04	5: 05	04	5: 21	12	5: 29	19	5: 33	30
	n=37	n=26	n=38	n=25	n=38	n=25	n=38	n=26	n=30	n=23
6. Pricing: e.g. pricing and profit controls, reference pricing	1: 80	88	1: 59	62	1: 34	35	1: 20	26	1: 26	32
	2: 15	12	2: 24	23	2: 37	38	2: 35	37	2: 16	20
	3: 05		3: 07	15	3: 12	20	3: 18	19	3: 23	20
	4:		4: 07		4: 12	08	4: 15	15	4: 13	12
	5:		5: 02		5: 05		5: 13	04	5: 23	16
	n=40	n=26	n=41	n=26	n=41	n=26	n=40	n=27	n=31	n=25

7. Dispensing (pharmacy level): e.g. generic substitution, remuneration	1: 85	92	1: 66	73	1: 44	42	1: 38	26	1: 42	29
	2: 10	08	2: 27	28	2: 34	46	2: 30	52	2: 26	42
	3: 05		3: 05		3: 17	12	3: 20	19	3: 13	08
	4:		4: 02		4: 02		4: 10	04	4: 10	08
	5:		5:		5: 02		5: 03		5: 10	13
	n=40	n=26	n=41	n=26	n=41	n=26	n=40	n=27	n=31	n=24
8. Prescribing: e.g. prescribing guidelines, budgets	1: 90	100	1: 61	85	1: 41	31	1: 26	19	1: 29	17
	2: 10		2: 32	15	2: 34	62	2: 35	56	2: 23	29
	3:		3: 07		3: 20	08	3: 20	19	3: 23	29
	4:		4:		4: 05		4: 15	07	4: 16	13
	5:		5:		5:		5: 03		5: 10	13
	n=40	n=26	n=41	n=26	n=41	n=26	n=40	n=27	n=31	n=24
9. Post-licensing evaluation (comparative benefit/ cost effectiveness)	1: 73	88	1: 34	35	1: 17	08	1: 10	04	1: 16	08
	2: 23	12	2: 41	65	2: 29	42	2: 25	30	2: 13	13
	3: 05		3: 22		3: 39	50	3: 33	37	3: 13	21
	4:		4: 02		4: 07		4: 25	26	4: 35	42
	5:		5:		5: 07		5: 08	04	5: 23	17
	n=40	n=26	n=41	n=26	n=41	n=26	n=40	n=27	n=31	n=24
10. Reimbursement: by public payers, i.e. scope of benefit catalogue (including positive/negative list)	1: 90	96	1: 70	81	1: 43	50	1: 28	26	1: 32	25
	2: 10	04	2: 20	15	2: 38	38	2: 45	44	2: 28	42
	3:		3: 10		3: 15	08	3: 13	19	3: 22	17
	4:		4:	04	4: 05	04	4: 15	11	4: 10	13
	5:		5:		5:		5:		5: 06	04
	n=40	n=26	n=40	n=26	n=40	n=26	n=40	n=27	n=31	n=24

Will the following issues predominantly be regulated and implemented at a European level or at a national level? **Grey: highest score** 1=fully national, 2=predominantly national, 3=even or 50/50, 4=predominantly European, 5=fully European

The results of the experts' expectations largely confirm the findings of the literature review in terms of actual competences. Furthermore, they seem to continue the 'Europeanisation' trend as observed in the review of 40 years of pharmaceutical policy. When merging the results of table 17 with figure 7 (see Chapter 4) this becomes even clearer (see figure 8). In those fields where a shared competence between the EU and Member States exists, the experts expect a shift towards European regulation of at least two points on the Likert scale between 2006 and 2025. In the field where the Member States have more competence, only a one point shift towards Europe is expected and the overall results suggest that these issues remain predominantly regulated at the national level. One exception is the issue of post licensing (part of the reimbursement decision) which shows a higher jump of two points towards a field of shared competence. The expectation of European collaboration projects initiated by the member state instead of on a European level could be an explanation for this. Section two of this Chapter will elaborate further on this issue.

Figure 8 Competences in the national pharmaceutical market combined with expected shift between 2006 and 2025 (rated 1-5) based on expert opinions



Rating: 1=fully national, 2=predominantly national, 3=even or 50/50, 4=predominantly European, 5=fully European

The expert opinion

When asked for their opinion a significant amount refrained, especially in the first round. It seems to illustrate the difficulties the respondents experienced in answering this particular question. Maybe one explanation is provided by a respondent who stated under his or her comments section: *'my opinion depends on the content of the policy, not where it is promulgated, and so that is why I have not expressed any opinion in that column.'* Although it provides a perception of the question, one can still state, irrespective of the contents of the policy, whether it is 'better' to regulate and implement certain issues on a national or a European level.

Furthermore, the experts' expectations seem to resemble the experts' opinion on the desired situation. That could mean two things. The experts (1) approve of the development of the European pharmaceutical market and agree on its course or (2) filled out the questionnaire suiting their own interests. Or as one respondent stated in the comment section: *'I have the strong feeling that the 'consensus' will depend on the interests of the responders and the mix*

of responders'. There could be a bias of course, coming from the background of the respondents but it is hard to see the interest a respondent could have in filling out an anonymous questionnaire on the future of the European pharmaceutical market, not used for any official policy making purpose, in a for his or her position favourable manner.

6.2 Filling in scenarios

The results of the Delphi questionnaire can now be used to construct three scenarios. The outcomes of the experts' view –as said before basically an extrapolation of current policy trends– will be used as the 'middle' and 'most likely' scenario, called the 'Expert Scenario'. This Expert Scenario will be contrasted with a more 'pessimistic' scenario and a more 'optimistic' scenario.

In the 'pessimistic' scenario, which will be referred to as the 'European Crisis Scenario', the European process suffers major setbacks, mainly caused by a stalling expansion process, a pervasive image problem, the public's lack of trust in European integration, which is all worsened by an enduring European constitutional crisis. These developments eventually lead to a return to national regulation and a freeze on the European process.

The 'optimistic' scenario, called the 'European Scenario', assumes that after the successful passing of the European Constitution, spurring a newly found élan and trust by the citizens in the European project, Member States increasingly 'suffer' from border crossing patients. This threatens the financial balance of their respective health care systems and action to counter this is required. The Member States gather and try to work out a deal on a European benefit catalogue. This leads to an Europeanisation of the various national health systems that ironically has not been instigated by the European Commission, but by Member States. In the next Chapters these scenarios will be elaborated upon.

6.2.1. The Expert Scenario

Basically, the Expert Scenario is an extrapolation of current trends. After initial progress using secondary legislation such as directives and regulations, a standstill in the harmonisation process is reached, mainly because of the dissonance between subsidiarity and

SEM. Instead, the European Commission now favours an approach of coordination of national results along the lines of the G10 recommendations, in which the European Commission acts more as a facilitator. The projects, actions and collaborations resulting from the G10 process, partially already in place or linked to existing programmes, unfold over the next five years, after that –also because national agendas converge more– larger harmonisation efforts in certain areas could be possible, even using secondary legislation.

In this scenario, the sectors where European Law has the largest influence –roughly the whole European pharmaceutical market minus the diverse national health systems– will slowly move towards a predominantly European level-regulated and implemented system. Those sectors of the health care system that fall mainly under the national competence remain a national competence and see hardly any change towards Europe. In the next paragraphs the scenario (see table 18) will be described.

Table 18 The Expert Scenario in numbers

Issue	Today	2010	2015	2025
Authorisation	3	3	4	5
Pharmacovigilance	2	3	4	4
Classification	1	2	3	3
Distribution	2	2	3	4
Advertising	1	2	2	3-4
Pricing	1	1	2	2
Dispensing	1	1	2	2
Prescribing	1	1	2	2
Post licensing evaluation	1	2	3	3
Reimbursement	1	1	1	2

Will the following issues predominantly be regulated and implemented at a European level or at a national level? 1=fully national, 2=predominantly national, 3=even or 50/50, 4=predominantly European, 5= fully European

Authorisation

Authorisation will gradually turn from a field of equally shared competence into a solely European matter. The several national licensing agencies will only work for the EMEA based in London, and it is no longer possible to authorise a pharmaceutical for just one national market. A first step will be the removal of the exclusively national authorisation procedure by 2015. The various national licensing agencies will then serve solely as subcontractors for the London based EMEA. As a second step, the decentralised authorisation procedure will be phased out completely by 2025 after a gradual process of shifting certain therapeutic groups –

as done before with e.g. biotechnology products and orphan drugs– towards the centralised procedure.

Pharmacovigilance

The main 'European' instrument for pharmacovigilance is the Eudravigilance data processing network that came into effect in 2001, and which in November 2005 was modernised as a result of the Pharmaceutical review (European Commission 2001a). This network, in combination with the Clinical Trials Directive, seeks to harmonise and streamline the exchange of data between national licensing agencies, the EMEA and pharmaceutical companies. However, some complicating factors are the many different responsible authorities involved and the different procedures and responsibilities for products under the centralised and the decentralised authorisation procedure (ISI 2006). Therefore, the harmonising practice so far has been more successful for medicinal products licensed through the centralised procedure (CAPs), than for products licensed through the decentralised procedure. In the next years the European legal framework seeks to further harmonise regulation, pharmacovigilance practice, product information, communication and cooperation between Member States.

The first result will be an equally shared competence between Member States and Europe by 2010. In the following 15 years, the network will be enhanced and expanded. The abolishment of national authorisation and eventually the decentralised procedure will also provide a harmonisation boost and simplification for the system in favour of Europe. This means that all national pharmacovigilance systems will start working according to the same protocol and systematic by 2015, under the auspices of the EMEA, but leaving the national institutions largely intact.

Classification

Under Title VI of the Community Code relating to medicinal products for human use, criteria are set which determine whether a pharmaceutical should be classified as a prescription-only medicine (POM) or an over-the-counter (OTC), non-prescription drug. So far, however, these criteria are applied nationally. Also national variations exist as some countries split the OTC category into a Pharmacy supervised list (P) and General Sales List (GSL). Thus, one could say that the regulatory overhand lies in the Member States.

The European Commission, nevertheless, regards a more flexible classification process, in particular where it concerns moving medicinal products from POM to OTC status, as essential

for a competitive non-prescription market. Therefore the European Commission will use all its influence to implement the actions as proposed in the G10 recommendations in the next 5 years. These recommendations include allowing the use of the same trademark for pharmaceuticals moved to non-prescription status and stimulate Member States to review these switching mechanisms.

Next, starting around the year 2010, 'classification' will develop into a field of shared competence. An amended classification directive introduced between 2010 and 2015 will then establish the categories POM, P and GSL. In other words, the Directive follows the European trend of splitting up the OTC category. It is of course hoped that this would establish a more flexible and faster switching process, through which more pharmaceuticals get the non-prescription status (either P or GSL), making more drugs directly accessible to the public, on lower level outlets such as supermarkets. It also includes mechanisms for industry to apply for reclassification. This directive will attribute to a further harmonisation and thus Europeanisation of the European pharmaceutical market. However, even in this scenario, the classification decision is still applied nationally, but it can be expected that national differences in what is on sale will become less distinct.

Wholesaling

The wholesaling sector will see a further European harmonisation and liberalisation trend. Still very much nationally dominated, it will develop into a Euro-dominated field. As yet, there is only a European directive setting criteria that have to be met by wholesalers, such as adequate premises, qualified staff and emergency plans for market withdrawal. These criteria, however, are enforced on a national level by very different national authorities, varying from federal states (Germany) to a national medicine agency (Finland) and the health inspectorate (Netherlands). A first step will be more liberalisation Europe-wide through the workings of competition law. A regulation will make the supervision of wholesaling a European matter, the responsibility of the EMEA. The national competent authorities will then operate under the supervision of the EMEA.

Advertising

Although there is a directive that prohibits public advertising of prescription only medicines (POMs), the differences stemming from nationally applied classification decisions makes it a predominantly national field. Also, Member States decide themselves on the methods they use for controlling pharmaceutical advertising and the level of the penalties for breaching their

national rules. As a consequence of an overall trend towards a more liberal European pharmaceutical market, as favoured by the industrial policy leaning European Commission, advertising will change into an evenly shared competence sector.
More therapeutic groups will be open for direct consumer advertising around the year 2015, mainly through the working of the classification system and there will be more harmonisation in the methods for controlling pharmaceutical advertising and penalty level. As a consequence of this development, there will be more convergence in advertising between countries by 2025.

Dispensing, pricing, prescribing and reimbursement
Regulation concerning dispensing pharmaceuticals to the public, pricing, prescribing and reimbursement mainly takes place within the national health system, where the competence lies mainly at the national level and Member States decide how they regulate this, e.g. on a national level or devolving it to the regions. Therefore, the consulted experts expect not much European influence over the next years and the regulatory frameworks will for the largest part remain a national competence. As the Member States' policy in general takes a more health policy leaning perspective, it can be expected that the emphasis remains on cost containment, that more cost containment measures will be adopted and that these cost containment strategies used throughout the EU show more convergence. In concrete form this would mean more stringent pricing regimes, increased use of generic substitution especially in 'immature' generic markets, conservative prescribing through the use of guidelines, but also increased requirements for (and use of) economic evaluations (post-licensing evaluation) when taking reimbursement decisions. However, some Europeanisation is expected, but that does not have to mean much more than increased cooperation between countries, maybe even supported or facilitated by the European Commission where it serves its public health goals, or suits its market liberalisation agenda. Increasing the degree of generic penetration, for example, could curb the national budgets, but could also provide opportunities for the European Commission in promoting and facilitating a competitive European generic market.

The European Commission's 'limited' competence in the national systems does not mean that the Member States have full control over national pricing and reimbursement schemes. Some of the pricing and reimbursement schemes presently in force in Member States can have strong remit over the entire pharmaceutical market, i.e. 'outside' the various national health systems. The European Commission respects the authority of Member States in their national

health systems and respects their stake in protecting their health care budgets, but the Community pursues full competition for medicines neither purchased nor reimbursed by the State, i.e. categories of medicines that are not reimbursed, often non-prescription drugs, and those pharmaceuticals provided outside the state sector (private hospitals etc). This should result in a competitive EU-wide single market for non-reimbursed medicines with a pan-European price, with less interference from Member States' regulations.

The definition of what belongs to the national system, i.e. where does the national competence end and where does the European competence begin, will be redefined over the next twenty years. The Member States keep full competence in the market where regulation concerns controlling their health care budgets, e.g. through dispensing and prescribing regulation. This means restrictive pricing can only apply for reimbursed pharmaceuticals, and restrictive policies for dispensing and prescribing also only applies to reimbursed pharmaceuticals.

Post licensing evaluation

One of the more surprising outcomes of the Delphi is the expectation the experts have in the field of post-licensing evaluation. Although the increasing use and importance of clinical effectiveness and cost effectiveness studies as a 'fourth hurdle' for gaining access to a Member State's list of reimbursed pharmaceuticals is already a Europe-wide trend, which in this policy scenario will result in all Member States actively using the fourth hurdle, the experts expect a larger European role. However, apart from a facilitating role, this seems unlikely to be instigated by the European Commission. The more industrial-policy leaning European Commission is more interested in opening up the markets and more liberalisation than more restrictive controls, let alone putting restrictions in place that could eventually block off certain pharmaceutical products from being reimbursed in a certain Member Sate. Furthermore, the Commission recognises it is primarily a matter of national competence.

Maybe the outcomes are not as contradictory as it on first sight maybe appears. Not all European regulation and influence has to come from the European Commission. It is very well possible that the experts had more European-level cooperation between national governments and institutions in mind, i.e. initiated at the national level. Or, as one respondent rightly commented in the first round of the Delphi questionnaire *'where you say 'European' it does not necessarily mean European Commission, but it can be collaboration between the EU Member States'*. One can think of Europe-wide economic evaluations initiated by the National

Competent Authorities (NCAs such as NICE in the UK and IQWIG in Germany), even a structural cooperation between the NCAs. This cooperation will be increasingly possible as the national cost containment regulations and practices in this area show more and more convergence.

In their adoption of the G10 recommendations, the European Commission pleads for more exchange of national experience on health technologies (HTA), and is in this way hoping for more speed and transparency in national relative effectiveness systems. The EC supports this view through providing funding for EUnetHTA, the European network for Health Technology Assessment, which coordinates the efforts of 29 European countries including 25 Member States of the EU in evaluating health technology in Europe. In their reasoning, a patchwork of different national systems places a huge burden on industry and can delay access to the market. Hence, the European Commission will try to exert influence where it can, keeping in mind its limited competence, but with a different policy perspective (faster and easier market access and reimbursement) than the Member States (cost-containment through rational use of efficient pharmaceuticals).

6.2.2 The European Crisis Scenario

In the European Crisis Scenario we assume that a set of interrelated determinants come together in the upcoming 5 to 10 years, creating a very difficult environment for the EU pharmaceutical policy to progress. An ongoing constitutional crisis undermines the whole European process. After the failure of the ratification of the European Constitution through referenda in France and the Netherlands in May and June 2005 respectively, as well as the failed ratification of the Treaty of Lisbon (a revision of the European Constitution) through an Irish referendum in June 2008, the prospect of another failed attempt and its possibly fatal consequences cripple the successive EU presidencies. Although the successive Member States exercising the EU Council Presidency place an agreement on the European Constitution on the top of their agendas for the semi-annual European summits, the Member States remain divided among themselves how to solve the ongoing standstill. Instead, the Member States keep bickering over the European budget, ‘rebates’, the agricultural policy, democratic accountability, enlargement issues (Turkey in particular) and future visions of the EU. The presidency seems unable to find the right moment, the right political and economic opportunity, to come up with a feasible plan to start the ratification process anew.

Adding to the problem are low economic growth rates in the European Union and a cumbersome expansion with the new Member States. The Lisbon objectives to become 'the most competitive and dynamic knowledge-driven economy by 2010' seem further away than ever. They were already toned down, partially put on ice and branded 'unrealistic' and 'too ambitious', but now, hardly any European citizen believes in the beneficial effects of a Single European Market anymore. The new Member States (the EU12), but especially Bulgaria and Romania, do not provide the Union with fresh élan as maybe was hoped by the founding Member States. On the contrary, they slow down the harmonisation pace and have difficulty effectively transposing the 'acquis communautaire', the total body of EU law accumulated so far, into their respective legislative frameworks.

To make matters worse, a Vioxx-like scandal, of a medicinal product authorised through the European centralised procedure feeds the already present criticism on the EMEA and the European procedures. It is evident that these developments combined cannot remain without consequences for the European Union in regard to its power to carry out policies and its image to the public. It is against this difficult background, from a European perspective, that the European Crisis Scenario unfolds (see table 19).

Table 19 The European Crisis Scenario in numbers

Issue	Today	2010	2015	2025
Authorisation	3	3	2	2
Pharmacovigilance	2	2	2	2
Classification	1	1	1	1
Distribution	2	2	1	1
Advertising	1	1	1	1
Pricing	1	1	1	1
Dispensing	1	1	1	1
Prescribing	1	1	1	1
Post licensing evaluation	1	1	1	1
Reimbursement	1	1	1	1

1=fully national, 2=predominantly national, 3=even or 50/50, 4=predominantly European, 5=fully European (not based on expert opinions)

Authorisation and pharmacovigilance

In 2009, a through the centralised procedure authorised Statin drug called 'Cardax', sold and prescribed as a preventive cure to cardiac illnesses, turns out to have some terrible side effects. Cardax, which is introduced by company X, is authorised through the centralised procedure in which the company favoured Member State Y as a rapporteur state, expecting a

more rapid and favourable authorisation procedure than with other Member States medicine agencies. Data and market study led Company X to believe that they had the best chances to get their product approved through this Member State's agency. The new pharmaceutical soon emerges to be a blockbuster, with market shares up to 45% in Europe. Around two years after introduction it becomes clear that what the public was already speculating is true: the widely used product has life threatening side effects when used in combination with an ACE-inhibitor. Affected are mainly men above the age of 55, who after using Cardax show a significant increase of cases of cardiac arrythmias causing sudden cardiac death.

All European Member States are affected and a huge public outcry follows. Questions and motions are put forward in all national parliaments and the European parliament. Soon after this, already present criticism on the alleged industry-favouring EMEA aggravates. European public opinion and the majority in national parliaments hold the EMEA and the European Commission responsible and accuse the European Commission of neglecting its public health goals and favouring industry goals instead. In an attempt to appease the outraged and shocked public, Germany and France, two of the most affected Member States in terms of casualties of the disaster, announce to solely authorise new pharmaceutical products through their national authorisation procedures for an undetermined period of time. Furthermore, they announce a reassessment of all pharmaceuticals authorised through European procedures and a reassessment for all pending authorisation requests.

The German and French action is a major setback for the European Commission's pharmaceutical policy agenda and the EMEA and its procedures in particular. It precipitates a status quo for many years to come, with no actual change towards Europe. On the contrary, where possible, Member States place more emphasis on their national competences and practices. 'Europe' –and everything related to it– has become a heavily burdened term that Member States' governments and political parties rather avoid when courting the Euro-sceptic electorate. Moreover, solid economic growth in the European Area between 2015 and 2020 is seen as proof by both national governments and civilians that there is no necessity to revitalise the European process.

Pharmacovigilance, in accordance with the developments in the field of authorisation will become more regulated on the national level. The European Commission's plans to further

harmonise regulation, pharmacovigilance practice, product information, communication and cooperation between Member States will be put on ice.

Classification, distribution, advertising, dispensing, pricing, prescribing and reimbursement
The status quo seems to have the gravest effects for those fields that had the most potential to see a move towards Europe and to become Euro-dominated. Apart from authorisation and pharmacovigilance, classification, distribution and advertising could be mentioned in this regard. Regulation regarding pricing, dispensing, prescribing and reimbursement will develop along the lines of the Expert Scenario, in which these issues remain within the national competence. As a result this means that the national health policy perspective will dominate Member States' policies. This implies more stringent cost containment regimes, with restrictive pricing and reimbursement frameworks and a prominent role for clinical effectiveness and cost effectiveness. One can also think of increased use of generic substitution, rational prescribing and cost sharing.

The European Commission's 'limited' competence in the Member States health systems will not be acted upon as described in the Expert Scenario. This is mainly due to the general Europe-wide Euro-sceptic environment. This means that the European Commission will not take action in those fields that could be seen as a potential European field, i.e. regulation that applies (or has potential influence) 'outside' the boundaries of the national health system. This could, for example, be the case for pricing schemes or dispensing regulation applying to medicines neither purchased nor reimbursed by the State. Therefore, in the European Crisis Scenario there will be no developments towards a European competitive non-prescription market with less interference from Member State regulation and no developments towards an EU-wide single market for non-reimbursed medicines with a pan-European price. The discussion about the definition of what belongs to the national competence and what belongs to the European competence as described in the Expert Scenario is eagerly avoided.

6.2.3 The European Scenario

In the European Scenario (see table 20), we assume that an unexpectedly far reaching agreement on an actual European Constitution, i.e. not another treaty, combined with the highest economic growth rates since the 1990s in the European Union and unemployment rates steadily dropping from about 8% in 2006 to around 6% in 2011 gradually change the

overall Euro-sceptic public perception on the European Union. Furthermore, the new Constitution makes it easier to pass legislation as qualified majority voting is abandoned in favour of simple majority voting. Eurostat data show that an important factor of this relative success is the successful and much less cumbersome than expected expansion eastwards. The economic data show high domestic demand in the new booming accession countries, providing the EU15 Member States with new attractive markets to export to and invest in. A new European Commission plan drafted in 2010, embroidering on where the Lisbon objectives and the 'partnership for growth and jobs' left off, seeks to capitalise on this momentum. The new highly ambitious plan foresees more European harmonisation also with the use of secondary legislation.

Moreover, two developments in the European health care sector have far reaching consequences: first of all, better organised empowered patient groups, led by an increasingly aggressive Health Consumer Powerhouse, reaping the benefits of the latest EU case-law, spur a rise in European border crossing patients, who (independently, not as part of a cross border contract) seek reimbursement for health services abroad for what is often on the fringes of what is funded in the home state. Secondly, the growing importance of internet-pharmacies, enabled by favourable EU case law and less and less hampered by restrictive national regulation, has a catalyzing effect on border crossing pharmacy services.

Table 20 The European Scenario in numbers

Issue	Today	2010	2015	2025
Authorisation	3	3	4	5
Pharmacovigilance	2	3	4	5
Classification	1	2	3	4
Distribution	2	3	4	5
Advertising	1	2	3	4
Pricing	1	2	3	4
Dispensing	1	2	3	4
Prescribing	1	2	3	4
Post licensing evaluation	1	2	3	4
Reimbursement	1	2	3	4

1=fully national, 2=predominantly national, 3=even or 50/50, 4=predominantly European, 5=fully European (not based on expert opinions)

In this scenario, more patients will challenge refusals for reimbursement and combat legal uncertainties surrounding cross-border care. Successive rulings in the period until 2015 in favour of patients are the result, lowering unjustified barrier for providing and receiving care

abroad. In these rulings, the ECJ specifically addresses pharmaceuticals as both a service (prescription) and a good. Patients challenge long waiting times which, in the ECJ's view, are no longer justified as a tool for an efficient planning mechanism, even when national waiting lists targets may be met[46]. The patients challenge refusals for reimbursement for private providers[47] which takes away much of the (legal) uncertainty when visiting a foreign provider. Patients challenge refusals for treatment abroad that is not provided in the home state, while arguing that treatment offered at home is verifiably less effective than what is offered abroad[48]. That there is a looming potential for this was shown in the FP6 Healthbasket project which found that huge differences may exist in the way patients with identical conditions are treated across Member States, which can result in large differences in the choice of technologies, procedures, staffing mix and usage intensity (Velasco-Garrido 2006). This could then motivate European patients to use their legal options to seek statutorily paid health care across the border expecting to receive reimbursed treatment with e.g. newer technologies, or a more broadly defined treatment that includes services not included at home (Busse and Van Ginneken 2007). In this scenario, it becomes increasingly difficult for Member states to justify an authorisation refusal, even for treatments and services (including pharmaceuticals) that are not covered in the national benefit basket.

Patients also increasingly use the Kohll/Decker procedure (see Section 3.3.) to obtain pharmaceuticals that are listed in their home state, but dispensed by foreign pharmacies. Using this procedure, the patients even have a financial incentive to purchase (cheaper) pharmaceuticals abroad, which are then reimbursed with the higher home state tariff. Not only does this enable a profit, it may also imply, for certain Member States nationals, bypassing a co-payment. Favourable case rulings, initiated by patients demanding to be reimbursed at the higher home state rate, make this opportunity visible to the broader public.

All these developments combined strengthen and ease patients' opportunities to receive non-hospital care, thus pharmaceuticals, in a host state whether or not under the host state's reimbursement conditions. This undermines the European Commission's and Member States' attempts to secure national competence in the national health systems through a directive that

[46] As under the 2006 Judgement Watts, case C-372/04.
[47] This development is already visible in the 2007 Judgement Stamatelaki, Case C-444/05.
[48] According to the ECJ in Smits/Peerbooms, authorisation refusals on the grounds of effectiveness should be based on what is 'sufficiently tried and tested by international medicine' (evidence based medicine) when refusing an authorisation. In the Smits/Peerbooms case, the effectiveness of the sought treatments was deemed insufficient to justify reimbursement. Mounting a legal challenge would in theory stand a good chance when a treatment is verifiably better according to best medical evidence.

states that non-hospital care in another (host) Member State should be reimbursed according to the same conditions as in the home Member State.

The different patient groups in Europe observe this opportunity and draft lists of reimbursed services, pharmaceuticals and specific case law in all Member States to exploit the loopholes and uncertainties in cross-border care. In order to do this more effectively, the national patient groups organise themselves in pan-European patient organisations. This has a spike in border crossing health care as a result, mostly based on case law rather than Regulation 1408/71. The patient groups serve as information supplier for patients, using websites with examples and advice on in which situations it is beneficial to go abroad or not. Pharmaceuticals play a pioneering role in this development, cause through the increasing number of internet-pharmacies and internet-doctors, a patient does not physically have to go to another member state (which comes with extra costs that cannot be reimbursed), but can place his order from his own house, using his personal computer, whether or not using an internet-doctor from another country.

Member States argue, as done before, that border crossing patients pose a threat to the financial balance and solidarity of their health system through maintaining a balanced, accessible to all medical and hospital service through planning and contracting. Although this is a legally legitimate argument[49], it will have become too difficult and too late to reverse the arisen situation: countries with extensive benefit baskets and/or countries with cheap health services and pharmaceutical prices see an influx of foreign money coming from foreign health insurance systems (e.g. health insurers, NHS) and countries with more restrictive benefit baskets and/or high pharmaceutical prices will see the money leaking from their health system. In the end, the only rational answer to the new situation is for the Member States to sit together and come up with deal on a basic European benefit package with similar conditions for co-payments, i.e. to take out the incentive to go abroad. This would still leave room for additional benefit catalogues that reflect differences between Member States concerning the cultural and economic environment. The basic European benefit basket should limit people from seeking reimbursement for non-reimbursed services and costs in another country.

[49] As became clear from the 2001 ECJ's Judgement in Geraets-Smits and Peerbooms, case C-157/99.

Member States will also further open up their procurement and contracting mechanisms to foreign providers. The European health market, including the pharmaceutical market, becomes increasingly European in nature, in which providers, purchasers and patients increasingly interact on a European level.

Authorisation and pharmacovigilance

Under the European Scenario, authorisation and pharmacovigilance will develop along similar lines as under the Expert Scenario. Hence, authorisation will gradually turn from a field of equally shared competence into a solely European matter. The several national licensing agencies will only work for the EMEA based in London, and it is no longer possible to authorise a pharmaceutical for just one national market. The first step will be the removal of the exclusively national authorisation procedure by 2015. The various national licensing agencies now serve solely as subcontractors for the London based EMEA. As a second step, the decentralised authorisation procedure will be phased out completely by 2025 after a gradual process of shifting certain therapeutic groups towards the centralised procedure.

As for pharmacovigilance, the Eudravigilance data processing network that came into effect in 2001 in combination with the Clinical Trials Directive seeks to harmonise and streamline the exchange of data between national licensing agencies, the EMEA and pharmaceutical companies. However, complicating factors are the many different responsible authorities involved and the different procedures and responsibilities for products under the centralised and the decentralised authorisation procedure (ISI 2006). This is why the harmonising practice so far has been more successful for medicinal products licensed through the centralised procedure (CAPs), than for products licensed through the decentralised procedure. This will change mainly as a consequence of the developments in the authorisation procedures. The abolishment of national authorisation and eventually the decentralised procedure will provide a harmonisation boost and simplification for the system in favour of Europe. This means that all national pharmacovigilance systems will start working according to the same protocol and systematic by 2015, under the auspices of the EMEA, but leaving the national institutions intact. Around 2020 –and this is where the European Scenario differs from the Expert Scenario– an amendment of the existing regulation expands the competences of the EMEA and makes it the sole responsible body in Europe for pharmacovigilance.

Classification, Distribution and Advertising

Under Title VI of the Community Code relating to medicinal products for human use, criteria are set which determine whether a pharmaceutical should be classified a prescription-only (POM) or OTC drug. So far, however, these criteria are applied nationally. In the next twenty years 'classification' will develop into a fully European field. An amended classification directive introduced between 2010 and 2015 now establishes the categories POM, P and GSL Europe-wide. It mainly seeks to enable a Single European Market for pharmaceuticals and raise the number of non-prescription products, making more drugs accessible to the public through a flexible deregulation of pharmaceutical products. The classification decision will be the responsibility of the EMEA, for which national competent authorities are then contracted to give advice. Pharmaceutical industry will be encouraged to seek reclassification for their products through a new European reclassification mechanism. These directives will attribute to an almost complete harmonisation and thus Europeanisation of the European pharmaceutical market and the national differences relating to what is on sale will gradually disappear.

Also the nationally dominated wholesaling sector will see a further European harmonisation and liberalisation as expected in the Expert Scenario, albeit a bit further reaching: it will develop into a fully Euro-dominated field. As yet, there is only a European directive setting criteria that have to be met by wholesalers, such as adequate premises, qualified staff and emergency plans for market withdrawal. These criteria, however, are enforced on a national level by very different national authorities. A first step will be more harmonisation between national practices. A regulation will make the supervision of wholesaling a European matter, the responsibility of the EMEA. The national competent authorities will be under direct supervision of the EMEA, similar to the relationship between the national medicine agencies and EMEA where authorisation and pharmacovigilance is concerned.

Although there is a directive that prohibits public advertising of POMs, the differences stemming from nationally applied classification decisions make it a predominantly national field. As a consequence of the overall trend to a Single European Market for pharmaceuticals, advertising will change into a Euro-dominated field in order to facilitate the SEM. As a consequence a new regulation will make the monitoring of the advertisements and the penalties a European responsibility. As a result, the methods to monitor advertising of

medicinal products are harmonised and the level of the penalties when the directive is infringed will become standardised for all Member States.

Pricing dispensing prescribing reimbursement, post licensing evaluation

As seen above, those fields that traditionally have been the full competence of the Member States have to be adapted to the new European reality. This will force Member States to coordinate their pricing and reimbursement (including post licensing evaluation) decisions on a European level through collaboration of national competent authorities. Only in this way can they facilitate a European health market with free flowing services and people without directly giving up all their national competences. The harmonising effect also leads to more coordination in regard to regulation that concerns prescribing and dispensing of the pharmaceuticals. It is a gradual process in which first, between 2015-2020 a European health market will emerge, with Europe-wide free pricing for non-reimbursed medicines and generics, as well as a European basic reimbursement package, which takes out possible (financial) incentives to go abroad but on the other hand simplifies procedure for receiving treatment and pharmaceuticals abroad. This will be accomplished through collaboration instigated at Member States' level. In the years after this, more voices will be heard favouring larger European Commission involvement based on the principle of subsidiarity. The national collaboration process will have provided a high level of harmonisation in national practices and basically will pave the way for more European involvement. It will have become a logical step in the development of the Single European Market for medicines to arrange and organise things at a European level as it will have become the level best suited to achieve the objectives (the sufficiency criterion), and while it brings added value (the benefit criterion). Furthermore, it will build on the positive climate around the European Union in general and it has many organisational advantages. A Euro-dominated pharmaceutical market with a European reimbursement decision will be just one of the results.

The question then is, however, what policy perspective will dominate European Commission policy, i.e. restrictive pricing regulation or a free pricing for all pharmaceuticals? As of now, the European Union mainly has an industrial policy perspective, but that is largely the result of the factual competences the European Union has, which mainly stem from the free trade principles (see Chapter 3). When the EU will be handed new competences relating to health care policy and public health policy, the policy outcome is expected to change accordingly, and give a better, more balanced representation of Member States' overall perspective. Moreover, Member States are not expected to give up the competence in their national health

care systems when that would imply a radical change with their former policies. Hence, a more balanced policy, with a stronger health policy perspective, with innovative policies for restrictive pricing, reimbursing and prescribing regulation. In the end, one should not forget that it is the Member States that form the European Union.

PART III: ANALYSIS

7 ANALYSIS

In this analysis, the impact of the three pharmaceutical policy scenarios, i.e. the Expert Scenario, the European Crisis Scenario and the European Scenario, on the actors of the European pharmaceutical market will be systematically examined. Therefore, each future policy scenario (Part II, Chapter 6) will be confronted with the trends and characteristics for each actor as described in the literature review (Part I) as visualised in figure 1. The observed trends in the literature review are likely to be affected by different policy scenarios especially on the pace at which these trends evolve. In the next and last Chapter of Part III, the Discussion, research questions about what these scenarios imply for the provision of pharmaceuticals within the European Union and the competitiveness of European industry will be addressed, i.e. the goals of the European Commission in this sector.

7.1 Impact of the Expert Scenario

In the Expert Scenario, the supply side of the European pharmaceutical market in general will see a consolidation and harmonisation trend that 'trickles down' the pharmaceutical value chain. As a result, international consolidation where it concerns wholesalers and, at a later stage, pharmacies is a logical consequence of companies trying to keep up with the pharmaceutical industry and wholesalers respectively, in order to have a level playing field in which they face their respective suppliers on eye-level in an increasingly liberalised market. Various developments in European and national pharmaceutical policy reinforce these developments. One can think of the increasingly Euro-dominated authorisation procedures and classification decisions, but also the levelling effect of increasingly possible –while less hampered by national regulation and national differences– parallel trading combined with effective nationally set incentives.

Although the demand side of the market for a great part overlaps with the Member States' health systems, in which in the Expert Scenario the competence stays with the Member States, it is not immune to the European trend and is to a certain degree forced to adapt to the changing realities of the supply side. In the next paragraphs, the impact of the Expert Scenario on the various actors of the European pharmaceutical market will be analysed.

7.1.1 European pharmaceutical industry

In the 'Expert Scenario' the European policies mainly affecting the pharmaceutical industry are authorisation, classification, advertising, pricing, prescribing and reimbursement and post licensing evaluation. These will be discussed briefly to provide an overview of the impact the Expert Scenario has on the pharmaceutical industry, which includes the innovative industry, generic manufacturers and NBFs.

Authorisation

After the abolishment of the strictly national procedure, authorisation will be carried out through European procedures only by 2015. This implies that national differences in regard to what is available, how it is administered, packaging sizes et cetera, will gradually fade out. Pharmaceuticals tailored especially to the needs of the public of certain Member States disappear and what is on sale in a certain Member State will show no pan-European differences. This implies that especially generic manufacturers who are still strongly regionally embedded and mainly operate along national boundaries (Gambardella et al. 2000; Pammolli 2004) will have to look out for European partners to produce, market and distribute their generics since they will have to face increased competition from other European generic manufacturers. Hence, it can be expected that a consolidation trend as part of a general consolidation of pharmaceutical industry (see Chapter 2) can be expected to persist, maybe even accelerate due to increased competition. NBFs have been bound to the centralised procedure already, so there will be no impact on the way they seek authorisations –often indirectly through pharmaceutical multinationals– for their products.

Classification

The EU legislation concerning classification mainly seeks to facilitate a competitive non-prescription market. Already is the European OTC (P and GSL) market expanding in terms of value, volume and range of products, despite differences of detail in the exact products available and the regulations governing their distribution, supply and use (Bond et al. 2004). This is an interesting development for all manufacturers of non-prescription medicines, especially since the P and GSL category will presumably become applied Europa-wide between 2010 and 2015. Producers will have a large stake in getting their products switched from P to the –for the public– easier accessible GSL category. They will have the necessary mechanisms at their disposal to apply for a reclassification of their product, against Europa-wide criteria, albeit nationally applied. One can expect the industry to adjust to this

development, actually a lucrative opportunity, by developing new strategies and, for example, differentiating the range of their products and package sizes, all aimed at receiving the GSL status. It is also in line with the ongoing trend towards self-medication, and the increased expectation of Member States that citizens bear part of the health care costs themselves through self-medication (Bradley et al. 2004) and the European Commission's efforts to support a competitive non-prescription market as first articulated in its response (European Commission 2002) to the G10 report (European Commission 2001).

Advertising

In the Expert Scenario more therapeutic groups will be open for direct consumer advertising. In addition to this, a growing non-prescription market through deregulation also implies more pharmaceuticals for which direct consumer advertising is allowed, which could lead to an even further increase in advertising expenditures on top of the already very high marketing expenditures, which sometimes exceed the R&D budget (OECD 2008). On the other hand, the abolishment of the strictly national authorisation procedure, but also a more harmonised classification decision, will gradually remove national differences as to which pharmaceutical products are sold in which category in certain Member States. This increasing convergence will make it easier to instigate larger pan-European marketing campaigns, which can be expected to bring about synergy effects. Another advantage for the pharmaceutical industry, in this regard, will be the increased harmonisation in the methods for controlling pharmaceutical advertising and a harmonised penalty system instead of the old system that was fragmented along national boundaries.

Pricing, reimbursement post licensing evaluation and prescribing

Since the Member States will retain full control over their national health system where it concerns the state (publicly covered) sector, there will be more emphasis on cost control and curbing health care budgets, which is in line with the current trend (see Sections 4.2 and 4.3). Furthermore, the increasing convergence with regard to the methods used for cost control (Maynard and Bloor 2003; Guillén and Cabiedes 2003), the pharmaceutical products that are available and the use of economic evaluation and post licensing evaluation (through European collaboration of National Competent Authorities), are likely to result in reimbursement decisions which are increasingly taken along the same lines having similar outcomes. Member States that hitherto knew relatively free pricing (e.g. Germany and the UK) will also increasingly constrain prices for innovative drugs. Member States will then use the full

repertoire of volume and price measures in order to circumscribe the number and price of pharmaceuticals that are reimbursed through the system. This implies that it will get more difficult for mainly the innovative industry to win back their increasingly costly (through new technologies) investments in R&D –especially in those cases when the new pharmaceutical has no proven extra clinical or administering benefit. Furthermore, this has considerable consequences for the sequence in which manufacturers launch their products on the European market, i.e. countries with relatively free pricing first, as this influences the prices in other countries as well through price comparisons. In the literature review it became clear that the pharmaceutical industry is quick in adapting to new situations so they can be expected to come up with various strategies to counter this new reality. Apart from the already visible consolidation trend, one can think of even more emphasis on drugs with blockbuster potential (lifestyle drugs, diabetes, cardiac illnesses etc), a further switch to the USA and new cheaper emerging markets (e.g. new EU Member States, Asia) as locus of research and operating activities in search of increased efficiency and productivity, larger marketing expenditures and increased financing of (well disposed) clinical trials. Research has shown that pharmaceutical companies tend to go where there is a strong market (Pammolli et al. 2004; OECD 2008). It is interesting to note in this regard that some new Member States, e.g. Poland, Hungary, the Czech Republic and Slovenia, already show an increased specialisation in pharmaceutical manufacturing (Pammolli et al. 2004).

On the other hand, new opportunities will arise if only through the sheer size of the European market as a whole, in which all national markets are gradually opened up through EU law. What arises is a formidable market of 487 million people with especially in the EU12 Member States large growth potential. In this market, a liberalised OTC market with free price setting throughout the EU, later followed by an increasingly European generic market will arise in which manufacturers compete on price. This development will make especially these markets more competitive. For generic industry, chances lie in favourable national policies on increasing the degree of generic penetration and favourable EU policies on promoting the wide use of Bolar provisions to ensure faster market access after patent expiration (European Commission 2002). This tougher competition should spur the competitiveness of the European generic industry, and not ‘nurture’ inefficiency (Gambardella et al. 2000). Tougher competition can be expected also in the marketing of generic products. Innovative industry will try even more to retain market share using their brand and give it a strong position on the market prior to patent expiration.

7.1.2. Wholesalers

In the field of wholesaling the current trends of consolidation and integration (Clement et al. 2005) will be reinforced by increased harmonisation in national pharmaceutical policies and liberalisation of pharmaceutical markets. On the one hand, the areas in which European wholesalers can cooperate increase with every development that harmonises the national regulation concerning the distribution, use and supply of pharmaceuticals. Since the pharmaceutical products that are on sale in the various countries of the EU are expected to become increasingly similar, it is likely that wholesalers collaborate in the purchasing and distribution of pharmaceuticals. On the other hand, the merger and acquisition trend is of course not a voluntary one, but also precipitated by fiercer competitive pressures.

A minority of countries do not allow for short-line wholesalers, because it is thought to be in contradiction with the public interest when wholesalers only specialise on certain therapeutic groups or pharmaceuticals in their assortment (Taylor et al. 2004a).. However, also here, EU law will gradually open up these markets and limit national interference. This will add to the in some Member States observed trend of highly specialised wholesalers, carrying a limited range of products at very competitive prices (Taylor et al. 2004a), which are especially active in those markets that are expected to gradually turn predominantly European over the next two decades, e.g. the non-prescription and generic markets.

Member States show differences in their legal frameworks with regard to the distribution chain, also concerning integration. It can be expected that these differences will slowly dissolve through the workings of EU law. This eventually will make vertically integrated combinations in the pharmaceutical value chain, i.e. combinations between pharmaceutical industry, wholesalers and pharmacies, a widespread European practice. Furthermore, the observed merger and acquisition trend (Clement et al. 2005) will continue and have a levelling effect on the huge differences between wholesalers per capita in the various Member States. This will result in oligopolistic market structures, as already observed in the more developed EU Member states, in most Member States by 2015. The consolidation trend increases the purchasing power of the wholesalers, through which they will be able to negotiate more effectively with their suppliers.

Parallel trading is expected to become more well-established not only through favourable case law, harmonised markets, effective national incentives and smaller price differentials, but also

because larger wholesaler combinations can face the industry on eye level. Before, wholesalers where reluctant to engage in parallel trading fearing profit loss and a bad relationship with the pharmaceutical industry, of which they were highly dependent. Needless to say, the pharmaceutical industry is a known adversary of parallel trading because they fear profit loss in high priced countries (also see Section 3.5.2 where case law is discussed). This development contributes, together with other aforementioned trends with a harmonising effect, to more competitive pressure and a levelling effect on price differentials.

Although these large wholesaler combinations purchase pharmaceuticals on a European level, at first the supplier relationship with pharmacies will remain basically conducted on a national level through locally based subsidiaries. However, also here more border-crossing services are likely to develop when European markets for certain pharmaceutical groups (OTCs and generics pioneering this development) develop.

7.1.3. Pharmacies

As seen in the literature review, the future of the European pharmacies is strongly interwoven with the future of the wholesalers, and they will basically follow the same trends. The pharmacies have special key role in the value chain, being on the dividing-line of the private free market that supplies them and the public, heavily regulated market they serve. Since it is such a regulated environment (Paterson et al. 2003), there is tremendous opportunity here for market liberalisation, and the EU will push through its agenda wherever it can. Ongoing market liberalisation will make market-entry regulation easier, which enables other forms of ownership and new combinations in the pharmaceutical value chain. For example, through enabling non-pharmacists to open pharmacies, by gradually abolishing state monopolies where present, or allowing the takeover of pharmacies across national borders, the market will be opened up. The EU perspective does not need to conflict with the national agendas since cheaper pharmaceuticals, through lower profit margins for pharmacists are perfectly in line with national health (care) policy.

At present there are huge national differences as to how many pharmacies per million inhabitants, with differences up to 7 times as many within the EU15 (Paterson et al. 2003; Taylor et al. 2004a) but a strong consolidation trend looking to reap the merits of economies of scale will counter these differences to a certain degree and larger chains are the result.

Chaining will give the pharmacies a better negotiation position in their dealings with suppliers, but will also avail them in an increasingly cost-conscious environment in which they are confronted with increasingly stringent national cost-containment policies. One can think of Member States promoting generic substitution, but also direct negotiations between governments and pharmacy organisations, as seen in, for example, the Netherlands. At first, chaining takes places within national boundaries, but also here it is very likely that the international takeover trend visible in the pharmaceutical industry, and followed by the wholesalers, will eventually trickle down to the pharmacies as well. It seems likely that the in this thesis described case of DocMorris will be an important example of more to come.

Another significant development with catalysing potential for the occurrence of European pharmacy chains with European prices is the rise of internet-pharmacies. However, this mainly applies to the OTC pharmaceuticals and non-reimbursed prescription pharmaceuticals, i.e. for those medicines where the patient carries the financial responsibility. If an internet-pharmacy in Member State A offers certain POM pharmaceuticals against a lower price than Member State B, a patient in Member State B does not have an incentive to order the product in Member State B because his or her payer will reimburse anyway. It is important to mention that the European Commission supports a mutual recognition of pharmaceuticals in a proposed 2008 Directive for cross border health services. It could therefore be a different case when Member State payers start to develop (or are given the instruments and freedom to develop) policies that will give patients some participation in the discount they receive. This would be in analogy with similar constructions for pharmacists that are allowed to keep some of the discounts they receive when they manage to purchase medicines against a discount. One could think of lower contribution for their insurer.

However, in this scenario this seems unlikely since it could also threaten the domestic pharmacy sector, i.e. the national provision of medicines, and that is not in the Member State's interest. But, for OTCs and for costly non-reimbursed pharmaceuticals, for example anti-malaria prophylaxis, which is not reimbursed in most countries' insurance policies, it can become very profitable to look around (and possible if we assume mutually recognised prescriptions). In addition, in this particular field, i.e. outside the national, publicly-covered system, Member States cannot do much to control or regulate it. Patient and consumer groups could function as facilitators in making this possibility visible to the public. The competitive pressure internet-pharmacies impose on 'traditional' pharmacies can result in lower national

prices and in the longer term internet-pharmacies can have a levelling effect on European price differentials.

7.1.4 Demand side (medical care triad)

The demand side of the European pharmaceutical market will be faced with increased cost aware policies in order to keep health care affordable and accessible over the next twenty years and after. Member States can adopt similar strategies concerning pricing prescribing and dispensing to achieve this, as discussed in Chapter 4, but also new initiatives will emerge, often part of larger health care reforms that aim to restructure the funding of health care in general and introduce more market competition. This could be some form of managed competition with limited government interference. In this development, the payer/purchasers of health care (e.g. health insurer, sickness fund, Primary Care Trust) will have a larger stake in controlling health care costs and are likely to bear more direct financial responsibility herein. It is, therefore, very well possible that in the future payers will play a larger role in controlling pharmaceutical expenditures than at present.

It is also on this side of the pharmaceutical market where still the most divergence between Member States continues to exist. Whereas the supply side is less fragmented and increasingly organised on a European level, the demand side represents 27 different Member States, and thus 27 health systems. Furthermore, it represents a myriad of cultural and personal attitudes towards prescribing practices and pharmaceutical consumption. These differences exist not only nationally but also on a regional, cultural and individual level. This applies to both prescribers (doctors, GPs and physicists) and patients.

Prescribers

In general, taking into account the differences in consumption and prescribing across national and cultural boundaries, doctors will be under increasing pressure to prescribe rationally and by doing so, have a larger responsibility in controlling health care cost. It can be expected that their ability to prescribe what they deem appropriate will be increasingly challenged through guidelines, electronic formularies and the use of prescribing data. In this practice huge national differences exist between Member States (see Section 4.2.2), so there will be frontrunners and stragglers, but the trends are already visible. Also more Member States with high levels of prescription per capita will realise that there is huge potential for savings. The frontrunners in general are the western and mainly northern Member States, whose

prescribing policies show more innovative and restrictive policies in this regard compared to southern traditionally high consumption countries. These policies will be adopted by the EU 12 countries when their health care systems develop towards the EU 15 average in terms of quality. In twenty years from now, the differences per Member State will be levelled for the largest part. Another development will be the increasing loss of trust in the doctor patient relationship, also due to more power and information in the hands of patients with regard to accessing and using medicines (Bradley et al. 2004). This development, in combination with restrictive cost containment policies, will implicate tough times for the reputation of the medical profession. It will be in their interest that they work along to construct these formularies and policies. It could also lead to more international collaboration in general and more European collaboration in particular of professional medical organisations looking to safeguard their autonomy in prescribing as they see fit.

Patient/consumer

In an IAPO (International Alliance of Patients' Organizations) survey, including input from patients from ten EU Member States, the patients rated the timely access to the best treatment and information, and right to participate in decision at the individual patient level, and patient involvement in policy-making among their top priority (IAPO 2006). This is reflected in this scenario for the future of the European pharmaceutical sector. As described in Section 2.2.2, the doctor-patient relationship is changing which can be ascribed to developments in the patient's environment. Patients become more involved in choice of treatment and have various ways to access a sheer limitless amount of medical information, mainly through the Internet. Furthermore, the doctor–patient relationship is characterised by a strong information asymmetry, but this unequal relationship will be countered up to a certain degree through patient empowerment.

The myriad of European patient groups also will organise themselves better, nationally but also on a European level, to keep up with the Europeanisation trends on the supply side of the European pharmaceutical market in order to enable them to participate independently –and on eye level with other actors– in the decision making process on health matters in the European Union in general. In this situation, it will be of key importance that in this age of rapidly growing, freely accessible medical information, patient organisation groups, in dialogue with the relevant European and national institutions, play a pioneering role in the establishment of a standardised European certifying system for health information web sites of good quality,

with, for example, quality labels and a multilingual web portal. Already there are regional and national networks in place and others are developing, but in this scenario, the expectation is that around 2010, these networks should work toward some kind of standardised European system. This can all take place within the frameworks of the G10 medicines group plan concerning information to patients, the EU's e-Health action plan (European Commission 2004b), and the 2006 MedIEQ (Quality Labelling of Medical Web Content Using Multilingual Information Extraction) project, co-funded by the European Commission under the public health programme. However, patient organisations have to play a pioneering and pro-active role in this process.

In addition to this, in an increasingly cost aware environment, patients will be expected to have an increased responsibility in paying for their medicines and may be encouraged to care for minor ailments wit OTC remedies, paid for out-of-pocket (Mossialos et al. 2004). Apart from good information, this also further illustrates the need for powerful patient organisations that monitor developments that could have negative effects for the equity of access. Another development will be the expectation that patients will increasingly be subjected to marketing efforts from the pharmaceutical industry. Not just through direct to consumer advertising, a result of increased competition and a larger OTC market and more therapeutic groups open to advertising, but also through new ways, such as funding for patient groups (Herxheimer 2003).

Patient organisations are relatively poor and have little independent funding, what can make them easily seduced by the rich pharmaceutical sector. When these relationships exist, they must be fully acknowledged and open. All patient groups should have readily available guidelines, maybe standardised on a European level, on how to have relations with pharmaceutical industry. In this light, the funding of patient organisations recommendation from the G10 medicines group is a good idea. However, there are important issues at stake in this development such as equity of access, appropriate use and detection of adverse events (Bond et al. 2004).

Payers

Under this scenario, not much convergence in national practices with regard to insurance form is expected and national health insurance systems will develop in ways decided upon on a national level. In other words, this is rather the result of a general health care policy than the

impact of European pharmaceutical policy. Whether this is some sort of managed competition, under public or private law, or a NHS is up to the Member State. However, it can be expected that in most Member States, innovative policies will be developed to counter agency problems and by doing so, give them more responsibility in the containment of costs.

7.2 Impact of the European Crisis Scenario

The European Crisis Scenario foresees a gradual return to national competence where possible. The process of an increased Europeanisation and consolidation of the distribution chain will be halted by the shift towards national competence and less foreign competitive pressures as under the other scenarios. This will inevitably have grave effects for all the actors of the European pharmaceutical market, from which the supply side actors will be particularly affected. Changes and stagnation are therefore most visible for those fields that in the other scenarios see an Europeanisation trend, i.e. those fields that in the other scenarios have shared competences between EU and Member State. This includes authorisation, pharmacovigilance, classification and distribution. The fields where the national competence is predominant, will see a development that is similar to the expert scenario, but not in a European, but a national context. In comparison to the Expert Scenario, there will be more divergence between countries, resulting in frontrunners and stragglers that are further apart in the way they implement policies than in the Expert Scenario, where the European process has a strong harmonisation effect. In the following paragraphs, the impact of the European Crisis Scenario will be examined in detail.

7.2.1 European pharmaceutical industry

Authorisation, pharmacovigilance, classification and distribution

Under the European Crisis scenario, authorisation, pharmacovigilance, classification and distribution will gradually return to the national competence. The failure of the European authorisation procedures becomes clearly visible in the period between 2015 and 2020 when the EMEA and its procedures will be dismantled. What remains are 27 strictly national authorisation procedures with different protocols, different data exclusivity periods, a myriad of pharmacovigilance systems and a nationally applied classification decision based on domestically determined criteria. The diverging effect of these developments will have huge

consequences for the pharmaceutical industry and the way they bring their products to the national markets.

The larger 'traditional' innovative multinational companies historically already possess subsidiaries in most countries, often the result of mergers and acquisitions. These national subsidiaries and agencies will now have to concentrate on maintaining –or maybe even expanding– the capacity to file for authorisation procedures and meeting the requirements of the national regulatory frameworks. Hence, for innovative pharmaceutical industry this scenario implies higher administration costs and even more pressure on their R&D budgets compared to a scenario in which 'administration and industry friendly' European procedures emerge as the European standard.

On the other hand, one could think that it could also provide opportunities to 'exploit' pharmaceuticals in higher priced states, for example states in which the pharmaceutical industry is an important provider of jobs. Anyway, this will be difficult in the more developed EU 15 countries considering the assumption that developed European states will all be forced to adopt stringent cost containment policies in order to curb the health care expenditures and relieve the national budget. Interesting in this regard could be the development that some of the new Central and East European countries already show: a specialisation into pharmaceutical manufacturing (Pammolli et al. 2004). This would make them an interesting relocation subject for pharmaceutical industry. Not only as a production facility with low labour costs, but also as a growth market where national governments are willing to develop a favourable industry friendly climate, including lenient pricing regimes –tailored, however, to the purchasing power in these countries– to attract and retain big pharmaceutical companies.

The still very much nationally organised generic manufacturers will have the smallest burden to bear. The several national generic markets will not develop into a 'dynamic' Europe-wide generics market with a standardised regulatory framework. The lack of convergence and standardisation means that potential competition from other countries will face a serious barrier and disadvantage that varies from country to country, when accessing a national market. Through this, generic industry can hold on to their dominant national positions for a longer period of time than under the other scenarios. However, the concentration trend will still be inevitable, mainly as a result of pressure from national pricing regimes, but it could be severely slowed down due to less foreign competition.

Smaller pharmaceutical companies that do not a have an agency or subsidiary in the various European states and companies for whom the central European procedure was obliged (often small non-European NBFs) will have to initiate authorisation procedures in all the different European States which is a clear competitive disadvantage in their quest to get their products on the market. In this process, pharmaceutical outsourcing companies such as Parexel will play a key role and show incredible growth potential when their expertise and infrastructure will be consulted, but also increasing use of partnership with multinationals (e.g. 'biopartnering') seems likely.

This increased administration effort to cope with the various regulatory frameworks will imply extra costs and it is possible that not for every European country an authorisation procedure and the expected returns are estimated to be a profitable investment. Poorer and smaller European countries may be deprived of some new products. It is not unthinkable, however, that smaller countries follow the example of Luxembourg and will adopt other European countries' authorisation decisions. Also, smaller scale cooperation on authorisation between certain European states could prove to be a necessity to safeguard access to expensive innovative pharmaceuticals.

It is important to note that the lines between innovative, generic and NBF companies have become blurred and will increasingly do so over the next twenty years. Hence, combinations of the above described developments are possible.

Advertising

In the 'European Crisis Scenario' the national differences as to which pharmaceutical products are sold in which category in certain Member States are expected to diverge as a result of national variations in market authorisations and classification decisions. The increased divergence will make tailor made national advertising campaigns, much like the present situation, a necessity. Two leagues of countries will become visible.

The first group, consisting of the more developed EU15 countries, puts more emphasis on self medication as a means to cut costs and would therefore favour flexible deregulation of pharmaceuticals. The populations of these countries have years of experience with this increased responsibility. Hence, the number of non-prescription pharmaceuticals open to

advertising is likely to increase. The ban on advertising for POMs will be prolonged, since it is assumed to stimulate the demand for expensive POMs.

The second group will mainly consist of Eastern and Central European countries with less developed health care systems. The populations are not as used to a culture of self medication, might not be aware of its dangers, and will therefore be protected by conservative classification decisions, i.e. pharmaceuticals are more likely to be kept on POM or (rather) P status. However, as assumed before, the Eastern and Central European countries are interested in attracting pharmaceutical industry as a locus of manufacturing and innovation. It could mean that to please the research intensive pharmaceutical industry is enticed with lenient advertising regulation. Concretely, this could mean that certain POMS are open to advertising. In this case the governments make a health/industry policy trade off in favour of the pharmaceutical industry. This is comprehensible keeping in mind that these countries have strong growth economies combined with not fully developed health care systems where the health budget does not pressure the national budget to the same degree as in 'western' European countries. Anyway, in both groups there are opportunities depending on which state and therapeutic class and overall spending on advertising will likely increase.

Pricing, reimbursement, post licensing evaluation and prescribing

As far as regulation within a state's health care system is concerned, the European Crisis Scenario will develop along the same lines as the Expert scenario. However, there are two major differences. First, in the Expert Scenario we assume that the pharmaceutical markets show convergence through the harmonising effects of increasingly Europe-dominated regulation for authorisation, pharmacovigilance, classification and distribution. This is not the case in the European Crisis Scenario where these markets are expected to develop in ways that increase the differences between them, which also restricts the opportunities to collaborate. Secondly, in the European Crisis Scenario, as opposed to the European Expert Scenario, the influence of EU legislation is not a factor of importance anymore. This means that there is no European liberalisation of the markets outside the state sector, hence no development towards a competitive European non-prescription market and no movement towards some sort of competitive European generic market. As a result, the European states will have strong remit over the 'entire' national pharmaceutical market (e.g. as described in Sections 4.2 and 4.3 respectively).

As described before and building on current trends (see Sections 4.2 and 4.3), it is expected that developed European health care systems will take a stronger health policy perspective in which containment of costs is key and that the newer less developed European States, mostly Eastern and Central European Countries are more likely to make a trade-off in favour of industrial policy. This is an assumption that requires strong economic growth in these countries and initial investments in the access to health care before switching to a stronger industrial perspective, since as of 2008, many Eastern European countries often have systems where patients are struggling with comparably high co-payments (e.g. Poland, Slovenia, Estonia).

In the former, we see the trend as described in the Expert Scenario, which means that the trend of copying methods used for cost control (Maynard and Bloor 2003; Guillén and Cabiedes 2003, of which economic evaluation, generic penetration and restrictive pricing will be expected to become integral parts, will set the standard. This implies that it will get more difficult for mainly the innovative industry to win back their –already accelerating in terms of costs– investments in R&D. In general, the aforementioned factors will not create a favourable long-term environment for the innovative pharmaceutical industry (including NBFs) in the EU 15 countries and further relocation of operations seems the cure.

In the latter, new opportunities for pharmaceutical industry will arise in the booming new European countries where favourable reimbursement and pricing policies only add to the already attractive emerging economies with low labour costs, growing markets as well as an abundance of well educated scientists and engineers. In this scenario, the relocation from the EU15 towards the USA and the Eastern and Central European Countries and other (comparable) emerging economies (e.g. in Asia) might take place with an accelerated pace.

For more nationally organised generic industry chances lie in favourable national policies on increasing the level of generic penetration. In this scenario they could be one of the winners, with less foreign competitive pressure as markets are diverging and governments with which their interests (generic penetration) are aligned.

7.2.2 Wholesalers

For wholesalers, this European Crisis Scenario will not have grave consequences on the short term. It does mean however, that the consolidation trends among European wholesalers towards pan-European wholesalers will be hindered as compared to the Expert Scenario, in which the current trends of consolidation and integration (Clement et al. 2005) will be accelerated through increased harmonisation in national pharmaceutical policies and EU law opening up national pharmaceutical markets.

The differences that Member States show in their legal frameworks with regard to integration, mainly where the wholesaler-pharmacist relationship is concerned, will not gradually dissolve, but will develop according to the policy objective in the respective country. In other words, some countries will implement –if not already in place– market liberalisation policies similar to those emanating from European Law, resulting in large vertically integrated combinations in the supply chain, whereas other countries will keep or increase the restrictions in their legal framework.

The observed horizontal integration trend will have a levelling effect on the huge differences between wholesalers per capita in the various Member States. However, the huge national differences will not disappear at the same rate as under the Expert Scenario. The strictly nationally regulated health systems will make it easier for wholesalers to retain their leading national positions for a longer period of time. 'Going abroad' is not yet a competitive necessity and does not have the same (financial) advantages as under the other scenarios, where collaboration in more fields, e.g. purchasing, storing, marketing and distribution, is possible.

Nevertheless, depending on the state of the development of the national pharmaceutical market, the national wholesaling market will show an increasingly oligopolistic structure. In this process there are frontrunners that as of today already reached this stage (mainly 'former' EU15 northern countries), a midfield (southern Europe) and trailers (new accession countries). Pan-European collaboration between the developed nations with similar frameworks remains attractive on a smaller scale and scope.

The operating environment for parallel trading will become more difficult and complex. Since market authorisations are granted on the national level, the differences concerning what is on sale (e.g. packaging sizes, administering form) vary between countries, which will increase

the impediments to import pharmaceuticals that are on sale in another country. Furthermore, it depends on the national framework of a certain country whether parallel trading is allowed. Where legally permitted, the wholesale combinations that do engage in these activities mainly operate in a national setting in this scenario and, as a result, have less negotiating power vis-à-vis the multinational pharmaceutical industry. Therefore they can be expected to encounter difficulties –bad relationship resulting in profit loss– with the pharmaceutical industry when they pursue parallel importing. The pharmaceutical industry would not appreciate a situation in which their products are purchased at a foreign subsidiary with lower prices. Even though the wholesalers are expected to hold on to their nationally leading role, they do face the difficulty of coping with an in contrast much larger, internationally oriented industry that has, therefore, a stronger negotiation position.

7.2.3 Pharmacies

There are huge national differences in the European Member States as to the number of pharmacies per million inhabitants and the regulatory environment they have to operate in (Paterson et al. 2003; Taylor et al 2004a). It is expected that under the European Crisis Scenario, depending on a certain Member State's policy perspective, more (national) market liberalisation will enable new combinations in the pharmaceutical value chain, with the hope that it increases efficiency and drives down the profit margins, i.e. a stronger health care perspective. One can think of the aforementioned trends towards chaining of pharmacies but also enabling non-pharmacists to open pharmacies of their own or takeover pharmacies. On the other hand, some Member States can be expected to take a stronger public health perspective and keep more restrictive regulations in place with regard to market entry, such as who can own a pharmacy (e.g. state monopoly or solely pharmacists), numbers of pharmacies (e.g. through economic needs tests and pharmacies relative to population numbers).

However, also under the European Crisis Scenario, up to a certain extent, larger chains are developing, which is hoped to give the pharmacies a better negotiation position in their dealings with suppliers, but also to cope with increasingly stringent national cost containment policies. One can think of Member States promoting generic substitution, but also direct negotiations between governments and pharmacy organisations.

Another significant development with far reaching potential is the emergence of internet-pharmacies. However, this development will take place mainly domestically since pharmaceutical markets and its regulations take a national course, which makes cross border internet-pharmacies virtually impossible.

7.2.4 Demand side (medical care triad)

The demand side of the European pharmaceutical market will be characterised through diverse national policies adapted to different national settings and priorities, representing a myriad of cultural, national, regional and personal attitudes towards prescribing practices and pharmaceutical consumption. Also here, the countries will show a division in two general groups along the same lines as described above.

One group, mostly consisting of the EU15 Member states, will follow the developments roughly as described under the Expert Scenario, i.e. they follow the ongoing trend and will expand their cost containment policies aiming at affordable and accessible health care through cost and volume measures. The strategies, new and existing ones, will often be copied from other countries and applied to their own domestic situation.

The other group, mainly the new accession countries, will tend to a policy trade off in favour of industrial policy. The reform of regulation after western European standards has been driven by the desire of EU access (Mrazek et al. 2004) and mainly included measures such as market authorisation, patent legislation, manufacturing standards, licensing requirements as well as drug pricing and reimbursement. The implemented cost containment measures have predominantly focused on reimbursement and pricing rather than measures affecting (rational) prescribing and dispensing (Mrazek et al. 2004).

Prescribers

In general, in the first group, doctors will face increasing pressure to prescribe rationally and thus, have a role in controlling health care costs, following the expectations of the Expert Scenario. Member States with high levels of prescription per capita will realise that there is huge potential for savings. It is likely hat the doctor's ability to prescribe what they see fit will be constrained through guidelines, electronic formularies and the use of prescribing data. In this process huge national differences exist between Member States, so there will be

frontrunners and stragglers. Add to this development the observed loss of trust of patients in their doctors (Bradley et al. 2004) and one can see that the medical profession will be under increased strain. It will be in their interest to cooperate to construct these formularies and policies. In the Expert Scenario international collaboration is foreseen at this point, but this cannot be expected to the same degree in the diverging national health systems of the European Crisis Scenario

In the second group, these volume measures will not be implemented to a large degree until the full range of pricing and reimbursement measures are exhausted and the health care systems are on EU15 level. In the meantime this practice nicely fits the governments' policies to provide an attractive manufacturing, operating and research base for the pharmaceutical industry. This is expected to take at least the next twenty years. The doctors will therefore enjoy more freedom in their prescribing habits and will not be subjected to (extensive) restrictive prescribing measures. However, the increasing loss of trust in the doctor patient relationship is a trend here, although not to the same degree as the consumers of more developed EU member States. This can be explained through (although gradually dissolving) differences in education levels, cultural attitude towards pharmaceuticals and information access.

Patient/consumer

In the first group of Member States, the patients will roughly see the same developments as in to the Expert Scenario, although not in a European context, i.e. circumscribed to the national setting. Hence, the doctor-patient relationship will change into a situation in which patients become more involved in choice of treatment and have various ways to access an abundance of medical information, mainly through the Internet. This will decrease the existing (strong) information asymmetry in the doctor–patient relationship up to a certain degree. Therefore, patient groups also will organise themselves better, mainly domestically, in order to avail them to participate independently in the decision making process on national health decisions. Furthermore, the development towards mainly nationally standardised certifying system for health information web sites of good quality will play a pivotal role. The patient groups will have to play a pioneering, pro-active role in that development. Already there are regional and national networks in place and others are developing. This will result in fully operational national systems by 2015. The development towards a European standardised system as described under the Expert Scenario will largely be put on ice.

Furthermore, in an increasingly cost aware environment, patients will be expected to have an increased responsibility in paying for their medicines and will be encouraged to care for minor ailments with OTC remedies, paid for out-of-pocket (Mossialos et al. 2004). This also further illustrates the need for powerful patient organisations –with access to the decision-making process– that monitor developments that could negatively affect equity of access to pharmaceuticals.

In the second group, the development towards full-fledged patient organisations still has a long way to go. The patients and their organisations will have to go through the same 'emancipation' process as in Group one Member States. This is expected to take longer due to cultural, political and economical factors.

Both groups, however, will be faced with increased marketing efforts from the pharmaceutical industry. Not just through direct to consumer advertising, which can be expected to be more common in 'group two' countries as a result of more therapeutic groups open to advertising, but also through new strategies, such as funding for patient groups.

Payers

As under the Expert Scenario, not much convergence in national practices with regard to the organisation of payers is foreseen. National health insurance systems will autonomously develop in ways decided upon on a national level as a result of discussions and decisions on their respective health systems that reflect country specific characteristics, e.g. concerning the economical, political and cultural environment. Whether this is some sort of managed competition, under public or private law, or a NHS is up to the Member State and not a result of the European Crisis Scenario.

7.3 Impact of the European Scenario

In the European Scenario, both the supply side and demand side of the European pharmaceutical market see a strong Europeanisation trend. On the supply side, this takes place at a faster pace and with further reaching consequences as under the Expert Scenario because pharmacovigilance matters as well as classification decisions are also decided on a supranational level. Member States at first will retain full control over their national health systems where it concerns the public sector. This implies more emphasis on cost control and curbing health care budgets, and thus an extrapolation of current trends (see Sections 4.2 and 4.3). When you add to this development the increasing convergence in methods used for cost control (Maynard and Bloor 2003; Guillén and Cabiedes 2003), the range of available pharmaceutical products and the use of economic evaluation (through European collaboration of National Competent Authorities), reimbursement decisions will increasingly be taken along the same lines. Furthermore, the market in general, the non-prescription and generic markets in particular, as well as the national benefit catalogues become more European in nature, also (forced) through border crossing health care. First step will be a European benefit catalogue that takes out the incentive for patients to go abroad for (reimbursed and/or in their home-state unavailable) pharmaceuticals. As a result, between 2020 and 2025 it will have become a logical consequence to arrange pricing, reimbursement, post-licensing and prescribing on a European level. What will result is an emerging SEM for medicines, with free movement of all pharmaceuticals, including innovative POMs, generic medicines and non-prescription drugs, all at pan-European prices (before taxes such as V.A.T).
On the demand side a development towards a European health market with European health insurers. For this, litigating consumers and border crossing pharmaceuticals play a pioneering and catalysing role. In the next paragraphs, the impact of the European Scenario on the various actors of the European pharmaceutical market will be described in more detail.

7.3.1 European pharmaceutical industry

In the ‘European Scenario’ the European policies mainly affecting the pharmaceutical industry are authorisation, classification, advertising, pricing prescribing and reimbursement and post licensing evaluation. As these fields for the larger part overlap with the developments under the Expert Scenario, these will be discussed briefly and more emphasis will be laid on the differences.

Authorisation

As under the Expert Scenario, authorisation will be carried out through European procedures only by 2015, and after a gradual phasing out of the decentralised procedure between 2015 and 2020, only through the centralised procedure by 2025. This implies that national differences with regard to what is on sale, how it is administered, how it is packaged, leaflet contents et cetera, will gradually disappear as newer products enter the market and in time substitute older ones. Pharmaceuticals tailored especially to the needs of the public of certain Member States gradually disappear and what is available in a certain Member State will hardly show differences across Europe. This practice will have profound influence on the innovative Industry as they are now dealing with one large market and only one market authorisation has to be filed.

This implies that especially generic manufacturers who are still strongly regionally and domestically embedded and mainly operate along national boundaries will have to look out for European partners to produce, market and distribute their generics, as they will have to compete with all other European generic manufacturers looking for a share of the (although growing) European market. Hence, the consolidation trend towards a competitive European generic industry can be expected to persist, maybe even accelerate. For NBFs there is no direct impact as the centralised procedure has already been compulsory for their products.

Classification

The EU legislation relating to classification mainly seeks to facilitate a competitive non-prescription market, which has been expanding in terms of value, volume and range of products. An amendment of the classification Directive first implements the P and GSL categories across the European Member States between 2010 and 2015. Then, and this is where the European Scenario differs from the Expert Scenario, a new regulation will make the EMEA the responsible institution for a centralised and binding European classification decision around 2020. This has, in interplay with the solely European central authorisation, a stronger harmonising effect on the pharmaceutical market than under the Expert Scenario. Producers will have a large stake in getting their products deregulated from P to the easier accessible GSL category, and will have the mechanisms at their disposal to apply for a reclassification of their product, at first through nationally applied Europe-wide criteria, and later, around 2020, through the European centralised classification decision. As under the Expert scenario, one can expect the industry to adjust to this development by developing new strategies and, for example, differentiating the range of their products, aimed at receiving the

GSL and P status. It is also in line with the ongoing self-medication trend, and the increased expectation of Member States, that citizens inevitably will have to bear a larger part of the health care costs.

Advertising

The harmonising effect of the centralised European market authorisation and classification decision will turn advertising into a Euro-dominated field, with a European monitoring and penalty system under the auspices of the EMEA. Moreover, more therapeutic groups will be open for direct consumer advertising, also as a result of an expanding non-prescription market and the deregulation of pharmaceuticals to P and GSL categories. Hence more pharmaceuticals will exist for which direct consumer advertising is allowed and possibly higher advertising expenditures will be the result. However, the even more rapid convergence trend as compared to the Expert Scenario across Member States will make it easier to instigate larger pan-European marketing campaigns which should enable efficiency gains for the marketing of pharmaceuticals that currently sometimes exceed the R&D budget (OECD 2008).

Pricing, reimbursement, post-licensing evaluation and prescribing

The European Scenario foresees increasingly converging national markets, with a limited number of reimbursed pharmaceuticals that go through a Europe-wide post-licensing evaluation. This national practice results in emerging and eventually fully European markets for non-reimbursed, generic and innovative medicines. This implies that it will get more difficult for mainly the innovative industry to win back their increasingly expensive investments in R&D especially when the new pharmaceutical has no proven extra clinical or administering benefit. It might become more lucrative to focus on OTCs with blockbuster potential or specific groups of lifestyle drugs. It will force pharmaceutical industry to abolish their market launching strategies (e.g. which Member State first?) as it will effectively become useless in a SEM with centralised reimbursement decisions where there are hardly possibilities left to manipulate and influence the prices. A further relocation to emerging economies (new accession countries, Asia) or more lucrative markets (USA) as a locus of research and operating activities, in search of productivity and efficiency gains, belongs to the alternatives and considerations. Also larger marketing expenditures and increased financing of (well disposed) clinical trials will seek to influence government and public opinion.

The European generic industry faces threats and opportunities in the emerging generic market. On the one hand, through favourable national policies, the degree of generic penetration is expected to rise and the market they serve will be extended to all Member States. On the other hand, fiercely competing foreign manufactures will attempt to attain a slice of the huge European market as well and prices will be driven down. The increasing competitive pressure will result in winners and losers, i.e. mergers and acquisitions, and an accelerated consolidation trend will become visible.

7.3.2. Wholesalers

For European wholesalers, similar to the Expert Scenario, the current trends of consolidation and integration will be reinforced by increased harmonisation in national pharmaceutical policies, liberalisation of pharmaceutical markets, increased competitive pressure and eventually the emergence of a SEM for medicines. The areas, in which European wholesalers can cooperate, increase with every development that harmonises the national situations. For example, wholesalers can be expected to collaborate in the purchasing (stronger negotiating position) and distribution of pharmaceuticals. This leads to a strategic relocation from the national market to the European market.

Furthermore, EU law will gradually open up the wholesaling markets and limit government barriers concerning market-entry. This will add to the development of –until now not everywhere legally permitted– specialised wholesalers, carrying a limited range of products at very competitive prices (Taylor et al. 2004a). The specialised wholesalers are initially mainly active in the markets that gradually turn European, first the OTC and generic markets, later the entire pharmaceutical market, i.e. including POMs. This has a levelling effect on pan European drug prices. Parallel trading is expected to become a widespread practice, playing a catalysing role in the harmonisation of pharmaceutical price levels, as observed in some studies (West and Mahon 2003; Enemark et al. 2006), through competitive pressure. This development contributes, together with other aforementioned developments with a harmonising effect, to the removal of European price differentials.

Furthermore, more market liberalisation will make vertically integrated combinations in the pharmaceutical value chain, i.e. combinations between pharmaceutical industry, wholesalers and pharmacies, a widespread European phenomenon. The strong consolidation trend has a

levelling effect on the huge differences between wholesalers per capita in the various Member States. This will result in oligopolistic market structures in most Member States by 2015.

7.3.3. Pharmacies

As seen before under the Expert Scenario, the future of the European pharmacies is strongly related to the future developments in the European wholesaling sector, and the pharmacies basically see the same trends. The EU will push through its market liberalisation agenda, helped by litigating (foreign) pharmacy chains in search for market share. This eventually deregulates market-entry regulation, enables other forms of ownership and makes possible new combinations in the pharmaceutical value chain. What emerges is a more harmonised European pharmacy environment, characterised by gradually abolished state monopolies (where present) and international consolidation as well as market entry and ownership by foreign pharmacy chains. There is no conflict between EU initiated market liberalisation with the national agendas since cheaper pharmaceuticals through lower profit margins for pharmacists is perfectly in line with national health (care) policy. This harmonising effect also combats the huge national differences as to how many pharmacies per million inhabitants exist, as it leads to a strong consolidation trend mainly through chaining. Chaining will give the pharmacies a better negotiation position in their dealings with suppliers. At first chaining takes places within national boundaries, but when national situations converge, and they converge faster than under the Expert Scenario, European chains will be the outcome.

Another significant development, as described under the Expert Scenario, with a catalysing potential for the occurrence of European pharmacies, and European prices is the strong rise of internet-pharmacies. Pharmacies have to compete with foreign pharmacies for market share which is possible as a result of a harmonised market. However, this in the beginning mainly applies to the non-reimbursed prescription pharmaceuticals, i.e. for those pharmaceuticals where the patient carries the financial responsibility, e.g. for OTCs but also costly non-reimbursed pharmaceuticals such as example anti malaria prophylaxis. Facilitators in making this opportunity visible to the public could be patient and consumer groups. The competitive pressure internet-pharmacies impose on ‘traditional’ pharmacies can result in lower national prices and in the longer term, internet-pharmacies from cheaper countries can signify a levelling effect on European price differentials.

However, when harmonisation of the pharmaceutical market in general advances and when payers receive more freedom to have influence on their own products and develop own policies, payers will encourage or obligate patients to get their POMs at selected, possibly foreign or self owned internet-pharmacies. Already there are pilots of insurers having their own pharmacies and an internet-pharmacy, with numerous advantages, will be a likely next step. It also embroiders on what is seen in the Netherlands, where plans exist to give the health insurers more responsibility for the purchase of pharmaceuticals. To build up the necessary expertise, taking over or opening up (internet-) pharmacies seems a logical step.

When pharmaceuticals become regulated at the European level by 2025, regulation will be put in place, stemming from former national policies, regulating the national provision of medicines. This will include a regulation that safeguards the public function of the pharmacies, i.e. that there is a minimum per million inhabitants or area.

Lastly, these developments have huge consequences for the responsibilities and scope of the pharmacist profession. Through deregulation of medicines and the emergence of internet-pharmacies, a personal advice on pharmaceuticals, one of the traditional roles of the pharmacist, will be increasingly taken away and put in the hand of the patients themselves. Furthermore, many future pharmacists will be employed instead of owning their own pharmacy. On the other hand they will increasingly obtain the legal instruments and responsibility to correct inaccurate prescriptions and substitute for (cheaper) generic equivalents.

7.3.4 Demand side (medical care triad)

The demand side of the European pharmaceutical market will see a markedly different development compared to the Expert Scenario. Empowered patient (groups) reap the benefits of favourable case law, which eventually results in a European health care market and a true SEM for pharmaceuticals. This, maybe unavoidably, precipitates the emergence of a European basic health care catalogue and, later on, a European health insurance market for patients, in which consolidated European health insurer combinations offer insurance policies open to all European citizens.

Prescribers

As in the Expert Scenario, there will be less freedom for the medical profession to prescribe, which comes combined with a loss of trust that create a difficult professional environment to work in. The various ways that Member States design their policies are discussed under the Expert Scenario. Those cost containment policies aimed at the prescribing habits of doctors will be increasingly adopted by less developed Member States when their rapidly developing health care systems touch EU15 level in terms of quality and quantity.

This implies hard times for the autonomy and reputation of the medical profession. It will be in their interest that they work along to construct these policies and exert as much influence as possible to alter the policy outcomes in their advantage. Therefore, since the European health care market will become increasingly European until it becomes fully European in nature, the doctors will have to organise themselves better, which shall lead to more European collaboration of European professional medical organisations looking to safeguard their autonomy in prescribing what they deem suitable for the patients.

Patient/consumer

Empowered patients and better organised patient organisation play a pioneering and crucial role in the development and realisation of the European Scenario and the emergence of a European health care market, which is described in more detail under the European Scenario in Chapter 6. The European patients and their organisations are an integral part of the European Scenario as it is they who interfere with the Member States' efforts to hold on to the competence in their respective health care systems, show a spike in pan-European patient mobility and challenge refusals for reimbursement at home for services incurred abroad, using favourable case law and harmonised European pharmaceutical markets to their advantage. Furthermore, it is the patients that speed up the development towards a European health system when they progressively use (possibly foreign) internet-pharmacies to purchase pharmaceuticals, initially non-prescription medicines and later gradually more POMs.

In their development towards a European partner that can participate independently and on eye level in the decision making process on health matters in the European Union, funding will be of key importance. In the European Scenario, this funding mainly stems from the European Union and national governments, which aspire to cut the increasingly observed partnership between patients and pharmaceutical industry. This will avail patient groups in

taking up a pro-active role in the establishment of a standardised European certifying system for health information web sites of good quality, which takes place within the frameworks of the G10 medicines group plan concerning information to patients, the EU's e-Health action plan (2004), and the 2006 MedIEQ (Quality Labelling of Medical Web Content Using Multilingual Information Extraction) project.

The need for information of good quality, about the product and its appropriate use, is strongly related to another challenge the European patient groups will face, namely the increased responsibility patients will receive in paying for their own medicines, also facilitated by flexible classification of medicines. This development can have negative effects for the equity of access and thus will deserve the full attention of the European patient groups.

The emergence of a SEM for medicines has influence over the price level throughout the EU. Lower priced countries that were formerly basically subsidised by higher priced countries (where industry made the larger share of its profits) are likely to see higher prices as new harmonised prices come into force. This could have consequences for the equity and access to medicines provided that economic and purchasing power differentials are still present throughout Member States.

Payers

The payer has many faces in the European pharmaceutical market: it can be a sickness fund, private insurer or an integrated part of a NHS; it can have public or private features; it can reimburse the patient or the provider. In the next twenty years there will be no convergence to the same extent as visible with other actors of the pharmaceutical market, not in the least because of the national health care structure and regulation they operate in. However, in most Member States there is a visible trend towards containing costs through health insurance reform, in which health insurers, receive more instruments for cost control, often through the introduction of some degree of managed competition, as for example in Switzerland, the Netherlands and Germany.

In the European scenario the payers are expected to develop more and more into European players in order to facilitate the European market when the basic European benefit catalogue becomes a fact. When patients observe that foreign health insurers offer cheaper policies covering the basic European health catalogue, they will (again!) insist on their right to free

movement of services and take out insurance from that foreign insurer. This of course, poses a large threat to the health insurers and the health care providers where they purchase their care. It is therefore likely that insurers increasingly act more cost aware in anticipation of the European health market, which is also in line with (hitherto) national cost containment policy. Hence, sickness funds and/or private insurers alike, will campaign to get more instruments to influence the expenditures in their health care system, for example through selective contracting with health care providers (already a widespread practice), but also through direct responsibility for the purchase of pharmaceuticals, thus influencing pharmaceutical prices. This will take place in anticipation of the Single European Market for health insurance that will gradually emerge afterwards, in which they are subjected to strong foreign competition and are increasingly expected to behave as market players. In this European health market, the European Union acts more as a facilitator that sets the rules concerning the benefit baskets, quality of care, patient rights and the accessibility, than as an actively controlling and managing institution. It may then turn out that this is easiest to regulate under a private set-up, which could lead to a privatisation of the European health sector. After that, the European consolidation trend, as mainly seen at the supply side of the pharmaceutical market, will become commonplace among health insurers.

DISCUSSION

Methodological discussion

To construct scenarios as robust as possible and to enhance the validity and reliability of these scenarios, a structured approach was chosen consisting of several fundamental components, following the methodology of the WHO commissioned handbook 'Health Futures' (Garret 1999). This approach is described in more detail in the introduction of this thesis. In addition, the input of multiple European Experts through the Delphi method was incorporated. Although groups are generally more accurate than individual experts, group processes can often lead to suboptimal judgements (Rowe and Wright 2001). Rowe and Wright (2001), therefore, defined several principles for using expert opinion in forecasting, which have implications for the selection of experts. The specific principles applying to expert selection are (1) use experts with appropriate domain knowledge, (2) use heterogeneous experts and (3) use between 5 and 20 experts. The former two were achieved by selecting the experts with the right (publishing) track record and by including expert questions in the survey to filter out those who estimate of themselves that they do not have the expertise. Even though the largest group among the addressees, and consequently among respondents, were academics (14 out of 27 in the second round), this group is highly heterogeneous in terms of background (e.g. law, economics, and public health) and expertise (e.g. varying from pricing/reimbursement to authorisation). In addition, other 'categories' of experts responded, including pharmaceutical industry (5 out of 27 in the second round), national government regulator (2 out of 27 in the second round) and 'other' (e.g. consultants, NGOs – 4 out of 27). With regard to the number of experts, this research consulted more than 20. According to research (Armstrong 1985) accuracy ceases to improve by higher numbers. However, this number will depend on the number of experts available but also on the nature and quality of feedback being provided (more in-depth feedback might suggest a smaller panel). In this Delphi application, which was set up to cover a very wide range of issues on different levels under very divergent spheres of influence, aiming for a high number of respondents was one of the key aims. That the respective answers of the respondents vary widely in their estimation of 'today' (2006) seems to underscore the difficulty in providing answers and justifies the consultation of a large number of experts. Maybe the relatively high percentage (34%) of respondents that bowed out after the first round provides further evidence of this assumption. The argument that a high number of participants may decrease the effectiveness of processing the information and giving feedback does not apply here, since feedback only consisted of the aggregated scores, i.e. no text, which had no influence on the feedback load. Furthermore, although 27

respondents participated in the second round, per 'issue' (e.g. authorisation, pricing) the respondents' sample varied from 23 to 25 participants, which is fairly close to the 'optimal' 20. Lastly, the chosen Delphi application was tested in a preliminary test round and described in detail in Chapter 5. The application can be repeated, albeit with possibly different respondents and another timeframe (i.e. not with 2006 as 'today').

It is advisable to be cautious when filling in scenarios and to be very aware of the methodological shortcomings of scenarios. A clear methodological limitation of a Delphi study is the difficulty to repeat and duplicate this study with the same experts and the same timeframe, which both affect its reliability negatively. Research has shown, however, that that a degree of reliability is possible using the technique e.g. Felsenthal and Fuchs (1976); Dagenais (1978); Kastein et al. (1993). The validity of a Delphi study depends on the quality of its design as much as on the nature of its panellists (Rowe and Wright 1999). The Delphi scenario is the main methodology when assessing possible futures and therefore, the main instrument to make prospective policies. The uncertainty and complexity surrounding the course of European health policy warrants a scenario study (also see Chapter 5 for more information on the choice and conduct of the Delphi method in this thesis).

The interpretations of the data generated by the Delphi questionnaire, which came in the form of numbers on a five point Likert scale, was done using the knowledge and findings of an extensive review of European and national policies in a historical perspective. Both this review and the Delphi information fed into the construction of these scenarios (also see figure 1). In the analysis, the impact of these scenarios was 'confronted' with the observed trends from the literature review with regard to the actors in the pharmaceutical (described in Chapter 1 and 2).

Discussion of outcomes

The impact of the three scenarios that have been constructed in the previous Chapters leads to a couple of obvious questions. First of all, how likely are these scenarios to unfold as described in Chapter 6? The experts showed convergence with regard to most regulatory issues as surveyed in the Delphi. They also fit the current set of trends, showing one exception for the issue of post licensing-evaluation. To realise alternative scenarios to this baseline scenario, the Expert scenario was contrasted with a more 'pessimistic' and a more 'optimistic' scenario. Compared to the Expert Scenario, the European Crisis Scenario is a far bolder

scenario, in which maybe rather far-fetched assumptions (e.g. constitutional crisis and a pharmaceutical disaster) leads to an unlikely but not impossible scenario. It is worth noting that it was a pharmaceutical disaster (Thalidomide) that spurred the first supranational involvement with pharmaceuticals in the European Community. Why could the same thing not happen in the opposite direction, i.e. starting from a relatively advanced European framework? The European Community has also changed since its foundation in 1957, not in the least with respect to its size, as it now encompasses 27 Member States. Maybe supranational legislation is no longer the appropriate level to regulate issues in such a huge market. The European Scenario may not be as far-off as the European Crisis Scenario. Its development mainly takes place along the lines of the Expert scenario, but at a much faster (harmonisation) pace, assisted by a Europe-positive climate. It is worth looking at this scenario as certain aspects, e.g. the strong pro-active role of the consumers leading to an increasing European nature of health markets, may well take place, and could therefore provide leads for a possible future (albeit maybe not in 20 years from now). The review of Part I of this thesis made clear that on the longer term major change is possible. In analogy, in 1965 it may have sounded very improbable that there would be European authorisation procedures only 30 years (1995) down the road.

The next question that arises is what are the main lessons to be learned from these scenarios, the Expert Scenario in particular? When looking at the scenarios, a couple of things become clear. The *supply side* of the European pharmaceutical market will likely see a consolidation trend that 'trickles down' the value chain and markets will increasingly be harmonised through EU legislation.

Despite European efforts to make the pharmaceutical industry more competitive, the future may not alter much in the current problems facing the *innovative industry*. In none of the scenarios it seems likely that there will be much change with regard to less restrictive pricing and reimbursement decisions, i.e. less opportunities to retrieve investments, in the richer countries of the EU. The expectation that post licensing evaluation will become widely used also through more European collaboration of national competent authorities (e.g. NICE, IQWIG and Commission de Transparence) will –to say the least– unsettle the European innovative industry. On the other hand, the sheer size of the European market, combined with increasingly European authorisation and classification decisions making way for synergy effects regarding marketing and market launching, will make the EU a progressively

indispensable market for innovative industry. If the EU seeks to foster the science base the pharmaceutical innovative industry provides, it will have to come up with innovative policies and incentives (e.g. for science in general, Framework Programmes) in coordination with Member States that can compensate for the less regulated pharmaceutical markets, in particular the USA, and the cheaper labour of emerging markets. This may require more than the hitherto proposed policies. For the *generic industry*, the outlook may be more positive. They will not suffer as much as innovative industry in bringing their products to the market. They will be helped by favourable generic policies, growing generic markets, especially the 'potential' of immature generic markets and will profit from faster market access through Bolar provisions. On the other hand, competition is likely to increase as a result of increasing foreign competitive pressure, leading to more (international) consolidation. The generic market may see a strategic shift from the national market to the European market. Only under the European Crisis Scenario, this development may be impeded to a certain extent. However, the EU goal of a competitive generic market with freer pricing seems a realistic aim for the future (as opposed to the market for POMs). Highly innovative *NBFs* have a vested interest in the continuous development of a European market but are faced with the same competitiveness problems as the innovative industry. The loss of the (obligatory) centralised procedure under the European Crisis scenario would effectively obstruct market access to (mainly smaller, less attractive) European countries as they are small in size and do not always possess the means to file a (national) authorisation procedure, for which they often seek a multinational partner. For them to survive, that is, avoiding takeovers, a large European market with centralised procedures is vital. However, biotech products are also subjected to the increasingly restrictive reimbursement decisions, which are increasingly based on cost-effectiveness studies. This makes them especially vulnerable considering the high R&D costs they have.

The European *wholesaling sector* is expected to see an international consolidation trend, both vertically and horizontally, and increased foreign competition. This implies that wholesalers not only purchase and distribute within national boundaries, but increasingly engage in cross-border purchasing and distribution. Hence, what before was known as parallel trade, will become well-established through favourable law and converging pharmaceutical retail markets. The wholesaling sector is well-advised to keep carving out their niche by differentiating their range of services (e.g. logistics) and search for partners, as pharmaceutical companies will increasingly seek to self-distribute their products, in the hope

of increasing efficiency. Another coping strategy is specialisation on a limited range of products at competitive prices. It is likely that EU market liberalisation will increasingly enable this practice. Only under the European Crisis Scenario they are able to retain their leading national position mostly owing to the more divergent national regulation and product range requiring national distribution channels.

Pharmacies will be faced with many challenges in the next twenty years leading to a completely different sector. They are increasingly the subject of European (market liberalisation) and national attention (huge profits, i.e. large cost-containment potential) and it seems likely that their 'golden days' will gradually come to an end on the assumption that the European Crisis Scenario does not materialise. The pharmacy market, as yet, is one of the most regulated sectors in Europe, leaving enormous potential for EU market liberalisation, also provided that (possibly foreign) newcomers litigate. The result will be different sorts of ownership (e.g. insurer-owned, non pharmacist-owned), new vertical combinations, chaining of pharmacies, abolishment of state monopolies and the emergence of internet pharmacies. The emergence of DocMorris in the German pharmacy sector could well be exemplary for many national pharmacy sectors across Europe of what they will have to cope with in the future. The increasingly harmonised range of products on sale in Europe will progressively enable cross-border pharmacy services, especially when mutual recognition of prescriptions becomes a fact. The internet pharmacies also pose challenges to legislators and policy makers as counterfeit drugs coming from rogue websites make its way into the distribution channel. The European Commission may use this example as an increased need for a SEM for medicines, as this would make pharmacovigilance more efficient. The Member States, on the other hand, will retain strong remit over pharmacy services concerning the way reimbursed medicines are dispensed, e.g. generic substitution. But one can also think of new incentives and measures to make cheaper pharmaceuticals attractive to consumers and to give payers the instruments and thus a financial stake in cheaper pharmaceuticals, in order to avoid that profits from cheaper pharmaceuticals remain in the distribution chain. This could be arranged, for example, through insurance policies that give discounts when cheaper pharmaceuticals (e.g. generic/parallel import) are used, or through enabling insurers to purchase their own pharmaceuticals and operating their own pharmacies.

The *demand side* of the European pharmaceutical market still shows huge differences between Member States as compared to the supply side. It will largely remain, especially for the part where it concerns reimbursed pharmaceuticals, within the national competence. This implies a continuation of observed trends.

The *prescribers* of pharmaceuticals will be under growing pressure to prescribe rationally and their freedom to prescribe as they see fit may be increasingly challenged through guidelines electronic formularies and prescribing data. Although significant differences exist between Member States in consumption patterns, roughly along the lines north-south and east-west, it is likely that these will cease to exist over time when new accession countries develop towards EU15 average, and when high consumption countries realise the cost containment potential of rational prescribing. Furthermore, the observed loss of trust in the patient-prescriber relationship is not likely to abate. Information is readily available on the internet and will only increase, unfortunately also from dubious sources. The strongly organised prescribers are well advised to organise at a European level as well, as their counterparts from other Member States see the same challenges regarding freedom to prescribe. Looking at the impact of the other scenarios, the European Scenario only reinforces the necessity to organise at European level, while under a European Crisis Scenario the need may be less essential or obvious.

The various *patients* groups should bolster their organisations, not only nationally but also on a European level, in order to participate more efficiently in the current European level discussions that may have far reaching consequences for them. This will also help to counter the strong information asymmetry, especially now supply side actors become larger and larger, and European affairs increasingly become important to the organisation and delivery of health care services. Only then can they fully reap the possibilities that an increasingly European market provides them with. First, patients should demand health information websites of good quality. Not in the least because it is likely that patients have more choices to make and will be increasingly subjected to marketing efforts by the industry often from dubious sources, with unclear distinction between patient information and advertising. They should play a leading role, in dialogue with relevant European and national policy makers in the establishment of a European certification system, which is possible within current initiatives and frameworks. Second, the increased expectations by national governments that patients bear an increasing part of the costs, especially as treatments are more expensive and

health expenditures are rising, stresses the need for patient organisations that monitor developments regarding quality and equity of access, and intervene in the public debate when needed at the highest level. It may be interesting to have a more thorough look at the European Scenario as this scenario deals with a more proactive role of consumers. There seems to be, as yet, potential to obtain cheaper and in the home state non-reimbursed pharmaceuticals through the cross-border delivery of pharmaceuticals. Patient groups should look into these opportunities and signal them to their members. They could play a pioneering role, also through litigation and articulation of these options, and force clarity in these frameworks. Whether this would lead to the emergence of a European health system with a European benefit basket, as described in more detail in the European Scenario depends on many factors. However, there are conceivable developments that could make this an inescapable solution.

This consideration automatically leads us to the role of the *payer* of pharmaceutical products. In the Expert Scenario and the European Crisis Scenario the impact of these scenarios on the payers is negligible. Payers will develop in ways decided at a national level. Their development is likely to contain already visible national trends to bring some form of managed competition in the insurance market, and therefore, the instruments that go along with it, such as selective contracting, more financial responsibility and competition for customers. Under most current frameworks the insurer has scant influence on the containment of pharmaceutical prices as they just pay what is prescribed. This could be solved by some of these innovative policies. It is probable that in the future payers in Europe will become more powerful players instead of merely administrative payer of services as still visible today in many countries. In addition, would the European Scenario materialise, pharmaceuticals play a pioneering and catalysing role in the emergence of a European health market and, possibly later, a European health insurance market in which international insurers offer health insurance policies for a European basic health basket. This could also provoke an international consolidation trend between health insurers.

What does all this imply for the *Member States*? Should they fear the continuous Europeanisation of the European pharmaceutical market? Although in the Expert Scenario the European pharmaceutical framework with regard to e.g. authorisation, classification (although nationally implemented) and wholesaling will turn European, the Member States fully retain the regulatory overhand on vital decisions in their respective health systems. For example, this

is visible with regard to pricing and reimbursement, as overwhelmingly expected by the experts. However, all national legislation that interferes with non-reimbursed medicines is likely to become under intensified European scrutiny. Furthermore, the regulatory framework for the pharmacy and wholesaling sector is expected to be liberalised over the next twenty years. Therefore, Member States should assess (to prevent them from being forced to at a later stage) their regulatory frameworks to bring it more in line with European competition law and the Four Freedoms. The expectation that apart from the non-reimbursed (e.g. OTCs) markets also the generic market will increasingly be liberated should motivate Member States to assess their pricing policies in this regard in order to facilitate a competitive generic market with free pricing. This basically also fits the national cost-containment agenda. In short, in the Expert Scenario it seems that all vital decision (e.g. pricing, reimbursement and classification decision) regarding their system –as far as it is publicly covered– are safeguarded. The expectation by experts that national competent post-licensing evaluation authorities will be increasingly regulated on a European level does not have to imply that this takes away the national competence to make their own decisions. Anyway, it makes sense for Member States to support this collaboration (as supported by current EU policy) as it will help them carrying out this task more efficiently –especially small Member States that lack funds to justify such an agency. If the European Scenario materialises, and a European health system develops as a result of external factors from outside the sphere of influence of Member States, Member States could be forced into a European collaboration on a basic benefit basket. This could be the start of a pan-European health insurance policy that could still leave room for national divergence through additional national catalogues, tailored to national needs relating to economic and cultural factors. Instead of categorically refusing the idea, it may be better to study it in order to be prepared.

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Note: All European Union law, including treaties, legislation, case-law and legislative proposals referred to in this thesis can be accessed at: http://eur-lex.europa.eu/

APPENDIX A

Delphi pre-test

From: Ewout van Ginneken

Subject: TU Berlin Dep. of Health Care Managment - (short!) Delphi pretest - please reply before JAN 11

Technische Universität Berlin

Delphi questionnaire 'European pharmaceutical policy'

NOTE: this Delphi round is a preliminary test round, to see whether the questionnaire is clear and understandable. Therefore, your feedback is more than welcome and can be given in the comments section at the end of this questionnaire. When results are satisfactory, they will be used and you will be approached again in the second round. When major changes in the questionnaire will be necessary, you will be approached anew. Your cooperation is highly appreciated and should not take more than a couple of minutes. Feel free to forward. Thanks!!

PLEASE REPLY BEFORE JANUARY 12

1 Introduction

This Delphi questionnaire is part of a research project on the future of the European pharmaceutical market. The Delphi technique is a procedure aimed at obtaining a reliable consensus of opinion from a group of experts through a series of questionnaires interspersed with controlled feedback (Garret, 1999). Aim of this Delphi questionnaire is to reach consensus among a group of selected experts on whether regulation in the European pharmaceuticals market will take a predominantly European or national course in the next twenty years. In order to achieve this, the questionnaire will be send to the experts several times, each time adding the results of the previous round. The individual results will not be attributed to the expert by name, i.e. are anonymous.

The survey starts off with questions about your category and expertise before going over to the actual Delphi part of the questionnaire. You can fill out the questionnaire in this document by replying to this message and by answering the questions in a new ('reply') mail. Make sure you send it to: praktikant@ww.tu-berlin.de. Feel free to forward this mail to your colleagues. As a beginning, two Delphi rounds are planned. Additional rounds can be scheduled later. Filling out the questionnaire – and possibly forwarding it– should not take more than a couple of minutes and would attribute greatly to this project.

2 General questions

Category of respondent
Please check the category that describes you best (e.g. use 'x').

Pharmaceutical Industry (innovative)		National government / regulator	
Pharmaceutical Industry (generic)		European Union	
Wholesaler		Academic	
Pharmacist		Consumer organisation	
Insurer/payer (NHS, sickness funds)		Other (feel free to specify)	

Expertise
Please answer using numbers 1 to 3.

1= fully
2= average
3= not at all

1. Would you consider yourself an expert in the field of European Pharmaceutical policy, both on the European and national level?	
2. Are you familiar with the current state of the European pharmaceutical market, including its actors and developments?	
3. Are you familiar with European Law in regard to European health care, in particular the European Commission's public health competences (as laid down in e.g. article 152)?	
4. Are you familiar with European case law, especially Kohll/Decker, Smits-Geraets/Peerbooms and Vanbraekel and its possible consequences?	

3 Delphi-questionnaire

Please fill out by using numbers 1 to 5 for each year and issue in the corresponding answering box. For category '**today**' give your estimation on the current situation. For category '**opinion**', give your own opinion: what would be desirable?

Will the following issues predominantly be regulated and implemented at a European level or at a national level?
1 = fully national
2 = predominantly national
3 = even or 50/50
4 = predominantly European
5 = fully European

Issue	EXPECTATION today	2010	2015	2025	opinion
1. Market Authorisation (Licensing)					
2. Pharmacovigilance (post marketing surveillance)					
3. Classification: Rx (Prescription only), OTC					
4. Distribution (wholesaling)					
5. Advertising: e.g. direct to consumer advertising					
6. Pricing: e.g. pricing and profit controls, reference pricing					
7. Dispensing (pharmacy level): e.g. generic substitution, remuneration					
8. Prescribing: e.g. prescribing guidelines, budgets					
9. Post-licensing evaluation (comparative benefit/ cost effectiveness)					
10. Reimbursement: by public payers, i.e. scope of benefit catalogue (including positive/negative list)					

Comments (not requested)**:**

Thank you for your cooperation.

Ewout van Ginneken, Reinhard Busse, Christian Gericke, Jonas Schreyögg
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APPENDIX B

Delphi round 1

From: Dept. Health Care Management
Subject: TU Berlin / Prof. Busse - (short!!) Delphi questionnaire - please reply before FEB 28!

Delphi questionnaire 'European pharmaceutical policy'

PLEASE REPLY BEFORE FEBRUARY 28 and PLEASE FORWARD / DISTRIBUTE

1 Introduction

Aim of this Delphi questionnaire is to reach consensus among a group of selected experts on whether regulation in the European pharmaceuticals market will take a predominantly European or national course in the next twenty years. The questionnaire will be send several times, each time adding the results of the previous round. The individual results will not be attributed to the expert by name, i.e. are anonymous. You can fill out the questionnaire in this document by replying to this message and by answering the questions in a new ('reply') mail. Make sure you send it to: praktikant@ww.tu-berlin.de. Please forward this mail to your colleagues and other contacts. Two Delphi rounds are planned (second round planned for early March). Filling out -and forwarding- the questionnaire should not take more than **a couple of minutes** and would contribute greatly to this project. Thanks for your help!

2 Category

Category of respondent
Please check the category that describes you best (e.g. use 'x').

Pharmaceutical Industry (R&D)		National government / regulator	
Pharmaceutical Industry (generic)		European Union	
Wholesaler		Academic	
Pharmacist		Consumer organisation	
Insurer/payer (NHS, sickness funds)		Other (feel free to specify)	

3 Delphi-questionnaire

Please fill out by using numbers 1 to 5 for each year and issue in the corresponding answering box. For category '**today**', give your estimation on the current situation. For categories '**2010**', '**2015**' and '**2025**', give your future expectation for these respective years. For category '**opinion**', give your own opinion: what would be desirable (also 1 to 5)?

Will the following issues predominantly be regulated and implemented at a European level or at a national level?

1 = fully national
2 = predominantly national
3 = even or 50/50
4 = predominantly European
5 = fully European

Issue	today	EXPECTATION 2010	2015	2025	opinion
1. Market Authorisation (Licensing)					
2. Pharmacovigilance (post marketing surveillance)					
3. Classification: Rx (Prescription only), OTC					
4. Distribution (wholesaling)					
5. Advertising: e.g. direct to consumer advertising					
6. Pricing: e.g. pricing and profit controls, reference pricing					
7. Dispensing (pharmacy level): e.g. generic substitution, remuneration					
8. Prescribing: e.g. prescribing guidelines, budgets					
9. Post-licensing evaluation (comparative benefit/ cost effectiveness)					
10. Reimbursement: by public payers, i.e. scope of benefit catalogue (including positive/negative list)					

4 Expertise

In order to possibly weigh the results, please answer these questions about your expertise, using numbers 1 to 3.

1= fully
2= average
3= not at all

1. Would you consider yourself an expert in the field of European pharmaceutical policy, both on the European and national level?	
2. Are you familiar with the current state of the European pharmaceutical market, including its actors and recent developments?	
3. Are you familiar with European Law with regard to European health care, in particular the European Commission's public health competences (as laid down in e.g. article 152)?	
4. Are you familiar with European case law, especially Kohll/Decker, Smits-Geraets/Peerbooms and Vanbraekel and its possible consequences?	

Comments (not requested)**:**

Thank you for your cooperation.

Ewout van Ginneken, Reinhard Busse, Christian Gericke, Jonas Schreyögg
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APPENDIX C

Delphi round 2

From: Dept. Health Care Management
Subject: TU Berlin / Prof. Busse - ROUND II Delphi questionnaire - please reply before APRIL 21

Delphi questionnaire 'European pharmaceutical policy' ROUND II

PLEASE REPLY BEFORE APRIL 21

1 Introduction

Thank you very much for your participation in the first round. Now we would like to ask for your opinion in this second round. Aim of this Delphi questionnaire is to reach consensus among a group of selected experts on whether regulation in the European pharmaceuticals market will take a predominantly European or national course in the next twenty years. In this second round questionnaire, the results of the first round are added. The individual results will not be attributed to the expert by name, i.e. are anonymous. You can fill out the questionnaire in this document by replying to this message and by answering the questions in a new ('reply') mail. If that does not work, please use the attachment. Make sure you send it to: praktikant@ww.tu-berlin.de. Filling out the questionnaire should not take more than **a couple of minutes** and would contribute greatly to this project. In this second round, you **only have to fill out part 3** of the questionnaire. Thanks again for your help!

2 Category

Category of respondents
Results first round after selection (no need to answer) n=41

Pharmaceutical Industry (R&D)	7	National government / regulator	3
Pharmaceutical Industry (generic)		European Union	1
Wholesaler	1	Academic	20
Pharmacist		Consumer organisation	
Insurer/payer (NHS, sickness funds)	1	Other (feel free to specify)	8

3 Delphi-questionnaire

Please fill out **after taking notice of the results of the first round** by using numbers 1 to 5 for each category and issue in the corresponding (grey) answering box. You can find the results (1 to 5) of the first round (in %) and number of respondents (n) for each answering category and issue under **Rnd1 (%)**. For category '**today**', give your estimation on the current situation. For categories '**2010**', '**2015**' and '**2025**', give your future expectation for these respective years. For category '**opinion**', we ask again to give your own opinion: what would be desirable (also 1 to 5)? You **only have to fill out the grey boxes**!

Will the following issues predominantly be regulated and implemented at a European level or at a national level?
1 = fully national
2 = predominantly national
3 = even or 50/50
4 = predominantly European
5 = fully European

			EXPECTATION							
Issue	**Today**		**2010**		**2015**		**2025**		**Opinion**	
	Rnd1 (%)	**Rnd2**	**Rnd1 (%)**	**Rnd2**	**Rnd1 (%)**	**Rnd2**	**Rnd1 (%)**	**Rnd2**	**Rnd1 (%)**	**Rnd2**
1. Market Authorisation (Licensing)	1: 08 2: 23 3: 45 4: 25 5: n=40		1: 2: 10 3: 45 4: 38 5: 08 n=40		1: 2: 3: 20 4: 50 5: 30 n=40		1: 2: 3: 05 4: 45 5: 50 n=40		1: 2: 3: 09 4: 25 5: 66 n=32	
2. Pharmaco-vigilance (post marketing surveillance)	1: 18 2: 49 3: 28 4: 05 5: n=39		1: 08 2: 15 3: 51 4: 23 5: 03 n=39		1: 05 2: 05 3: 33 4: 44 5: 13 n=39		1: 05 2: 03 3: 23 4: 44 5: 26 n=39		1: 2: 06 3: 22 4: 25 5: 47 n=32	
3. Classification: Rx (Prescription only), OTC	1: 38 2: 38 3: 15 4: 05 5: 03 n=39		1: 18 2: 38 3: 23 4: 15 5: 05 n=39		1: 08 2: 21 3: 31 4: 26 5: 15 n=39		1: 03 2: 21 3: 23 4: 28 5: 26 n=39		1: 10 2: 13 3: 10 4: 32 5: 34 n=31	
4. Distribution (wholesaling)	1: 41 2: 46 3: 08 4: 05 5: n=39		1: 15 2: 38 3: 33 4: 13 5: n=39		1: 03 2: 36 3: 33 4: 26 5: 03 n=39		1: 03 2: 26 3: 31 4: 26 5: 15 n=39		1: 03 2: 19 3: 35 4: 23 5: 19 n=31	
5. Advertising: e.g. direct to consumer advertising	1: 41 2: 19 3: 14 4: 22 5: 03 n=37		1: 16 2: 34 3: 18 4: 26 5: 05 n=38		1: 05 2: 18 3: 29 4: 26 5: 21 n=38		1: 03 2: 16 3: 24 4: 29 5: 29 n=38		1: 13 2: 17 3: 23 4: 13 5: 33 n=30	
6. Pricing: e.g. pricing and profit controls, reference pricing	1: 80 2: 15 3: 05 4: 5: n=40		1: 59 2: 24 3: 07 4: 07 5: 02 n=41		1: 34 2: 37 3: 12 4: 12 5: 05 n=41		1: 20 2: 35 3: 18 4: 15 5: 13 n=40		1: 26 2: 16 3: 23 4: 13 5: 23 n=31	
7. Dispensing (pharmacy level): e.g. generic substitution, remuneration	1: 85 2: 10 3: 05 4: 5: n=40		1: 66 2: 27 3: 05 4: 02 5: n=41		1: 44 2: 34 3: 17 4: 02 5: 02 n=41		1: 38 2: 30 3: 20 4: 10 5: 03 n=40		1: 42 2: 26 3: 13 4: 10 5: 10 n=31	

8. Prescribing: e.g. prescribing guidelines, budgets	1: 90		1: 61		1: 41		1: 26		1: 29	
	2: 10		2: 32		2: 34		2: 35		2: 23	
	3:		3: 07		3: 20		3: 20		3: 23	
	4:		4:		4: 05		4: 15		4: 16	
	5:		5:		5:		5: 03		5: 10	
	n=40		n=41		n=41		n=40		n=31	
9. Post-licensing evaluation (comparative benefit/ cost effectiveness)	1: 73		1: 34		1: 17		1: 10		1: 16	
	2: 23		2: 41		2: 29		2: 25		2: 13	
	3: 05		3: 22		3: 39		3: 33		3: 13	
	4:		4: 02		4: 07		4: 25		4: 35	
	5:		5:		5: 07		5: 08		5: 23	
	n=40		n=41		n=41		n=40		n=31	
10. Reimbursement: by public payers, i.e. scope of benefit catalogue (including positive/negative list)	1: 90		1: 70		1: 43		1: 28		1: 32	
	2: 10		2: 20		2: 38		2: 45		2: 28	
	3:		3: 10		3: 15		3: 13		3: 22	
	4:		4:		4: 05		4: 15		4: 10	
	5:		5:		5:		5:		5: 06	
	n=40		n=40		n=40		n=40		n=31	

Comments (not requested)**:**

Thank you for your cooperation.

Ewout van Ginneken; Prof. Dr. Reinhard Busse, Dr. Christian Gericke, Dr. Jonas Schreyögg
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