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Trade and Innovation: Pharmaceuticals

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Abstract

TRADE & INNOVATION: PHARMACEUTICALS

by

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Globalisation in the pharmaceuticals sector is entering a new phase. Many new drugs are marketed globally, and these revenues encourage further investment in research and development (R&D). The industry is undergoing substantial transition, with increased competition and downward pressure on prices. Moreover, there have also been widespread concerns that R&D productivity may be declining in recent years.

This study examines how various linkages between trade and innovation work in the pharmaceuticals sector, focusing on the role of globalisation in the current innovation challenges of the pharmaceutical industry. It finds that emerging economies are increasingly important markets for pharmaceutical companies and more active participants in the R&D process. While this is an important part of an effort to reduce R&D costs and to improve R&D performance by established multinationals, this also contributes to upgrading the R&D capability of emerging economies.

Various trade facilitating measures have been put in place at the international level, including tariff elimination under the World Trade Organization (WTO), plurilateral and bilateral regulatory harmonisation, mutual recognition and enforcement cooperation, and intellectual property protection. Given the growing participation of emerging economies in this sector, further involvement of emerging economies in these arrangements is likely to become more important to facilitate trade and globalisation of R&D.

JEL classifications: F13, F14, L65, O31

Keywords: pharmaceutical innovation, globalisation of R&D, WTO, emerging economies, tariff elimination, regulatory harmonisation, mutual recognition, intellectual property

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Executive Summary

This study on trade and innovation in the pharmaceuticals sector builds on the previous papers on trade and innovation by the Trade Committee, and most recently a study focusing on the chemicals sector.

Various linkages between trade and innovation are highlighted in this paper. First, global sales have always been an important source of revenue for large pharmaceutical companies, and the revenues from global sales have provided incentives and funds for research and development (R&D) investment for future innovation. Global sales of pharmaceutical products, in turn, mean global diffusion of advanced medical technology and benefit importers in terms of improved health, an essential basis for future growth and innovative capacity.

Whereas competitive pressure from new substitutes and generic drugs are putting pressures on the profitability of pharmaceutical companies, globalisation is providing new sources of innovation. More clinical trials are being carried out in emerging economies, and R&D activities are becoming more globalised. Organisational innovation has been taking place to improve performance of global R&D activities. Growth of emerging markets is providing new opportunities of global sales for pharmaceutical companies, and challenges to devise innovative marketing methods to penetrate non-traditional markets. mergers and acquisitions (M&As) involving emerging markets are gaining ground, in order to secure a foothold in these markets as well as to enhance R&D collaboration. From the side of the companies in emerging economies, M&As are an instrument to transfer skills and technologies to foster innovative capacity as well as to capture market opportunities.

The particular importance of trade in this sector is reflected in various kinds of trade facilitating measures specifically addressed to this sector. Most of the OECD members have bound their tariffs at zero for pharmaceutical products as a result of the Uruguay Round, and imports of pharmaceuticals to these countries are now essentially duty free. However, substantial tariffs remain in other countries, and a proposal for further tariff elimination in a range of healthcare products has been tabled in the current Doha Development Agenda.

Given the unique regulatory regime in this sector, a number of plurilateral and bilateral initiatives to address regulatory issues, going beyond the disciplines of WTO's Technical Barriers to Trade (TBT) Agreement, have been taking place, and considerable progress has been made in regulatory harmonisation, mutual recognition and enforcement cooperation. Over 50 guidelines have been completed under the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and implemented in the participating regions. The Pharmaceutical Inspection Co-operation Scheme (PIC/S) has been promoting common Good

Manufacturing Practice (GMP) standards, and the OECD has been implementing the Mutual Acceptance of Data (MAD) system which reduces duplicative testing.

Partnerships with the emerging economies are being sought in each forum in order to extend the geographical reach of the impact of these instruments. Moreover, globalisation of manufacturing and R&D processes by multinationals has made ensuring their compliance with the domestic regulatory standards a pressing issue. Many emerging economies, for their part, are seeking to adapt to the international standards with a view to establishing the credibility and the competitiveness of their industry, but a gap still remains. Regulatory cooperation involving emerging economies is likely to become more important to ensure compliance while facilitating trade and globalisation of R&D. Moreover, globalisation has created an opportunity to take a fresh look at the efficiency of the regulatory regime in order to maintain innovative activities and industrial competitiveness.

Intellectual property, most notably patents, is of critical importance for this sector. While there have been considerable concerns about the state of patent protection in some emerging economies, the situation has been significantly improving due to the trade-related aspects of intellectual property rights (TRIPS) Agreement, particularly the introduction of product patents for pharmaceuticals. Concerns remain, however, regarding the actual implementation of the patent regime in several emerging economies, and bilateral dialogues are being pursued between major players.

I. Introduction

1. Background and the purpose of the study

This study builds on the previous papers on trade and innovation by the Trade Committee, in particular OECD (2008a) and the more recent sectoral study focusing on the chemicals sector.[1] Even though the pharmaceuticals sector is often classified as a part of the chemicals sector, the sectoral study on the chemicals specifically excluded pharmaceuticals from its scope in its analysis of trade and innovation linkages because of a number of features that makes it distinct from the rest of the chemicals sector.[2]

The chemicals study shows distinctly high and still rising R&D intensity of the pharmaceuticals compared with the rest of the chemicals sector, with R&D being mainly directed toward product innovation rather than process innovation.[3] It also shows a high rate of growth in pharmaceuticals trade in the 1990s and the 2000s, at around 15% annually across income groups; in particular in high income countries pharmaceuticals trade grew twice as fast as in other chemicals subsectors.[4] Moreover, tariff elimination focusing on the pharmaceuticals sector has been agreed and implemented under the auspices of the World Trade Organization (WTO) by major players, whereas tariff harmonisation was achieved for the chemicals sector at large.[5]

There are a number of other unique features involving innovation in the pharmaceuticals sector. First, even though pharmaceuticals innovation has its roots in the chemicals revolution at the end of 18th century, there has been a major shift in the scientific basis of the industry toward life sciences during the past few decades. Second, regulatory approval is commonly a prerequisite for market entry for new pharmaceutical products, and pricing policies on pharmaceutical products are in place in many OECD countries (OECD, 2008b). Third, product innovation in the pharmaceuticals is an exceptionally long and costly process, typically taking more than 10 years and costing USD 1 billion on average to launch a new product.

This study aims to examine how various linkages between trade and innovation work in the pharmaceuticals sector. In particular, this study focuses on how globalisation plays

1. OECD Trade Policy Working Paper No. 103, www.oecd-ilibrary.org/trade/oecd-trade-policy-working-papers_18166873.
2. *Ibid,* Section I-3.
3. *Ibid,* Figures 9-10.
4. *Ibid,* Figures 2-4.
5. *Ibid,* Box 1. Tariff elimination for the chemicals sector, beyond harmonisation, is a subject of a negotiating proposal in the current DDA (Doha Development Agenda) negotiations.

its part in the current innovation challenges of the pharmaceutical industry. The structure of this paper is as follows: the remainder of this section illustrates the scope of the pharmaceutical sector and its industrial structure. Section II introduces the unique features of innovation in pharmaceuticals, and Section III examines the role of globalisation in innovation in pharmaceuticals. Section IV concludes.

2. Scope of the pharmaceuticals sector

Pharmaceuticals can be divided into three categories: in-patent drugs, out-of-patent drugs, and generic and over-the-counter (OTC) drugs (Tarabusi and Vickery, 1995). This categorisation is in accordance with the typical business models of pharmaceutical companies associated with the regulatory regime.[6] Pharmaceutical companies develop new products and seek regulatory approval, after which they put them on the market under patent protection as well as the regulatory process. After the patent expires, generic equivalents will enter into the market. Many pharmaceuticals are sold by prescription only, with 80% of pharmaceutical expenditure being for prescription drugs (OECD, 2008b), although the scope of prescription drugs and OTC drugs varies depending on national regulations.

The different characteristics of in-patent drugs and generics can be seen in the cost structure of the two sub-groups of companies (Table 1). Whereas R&D is one of the major cost factors for "originator companies" (those who sell a novel drug that was under patent protection when launched), manufacturing cost is by far the largest for generic companies.

Table 1. Cost structure of orginator companies and generic companies

Prescription medicines, % of annual turnover

	Marketing, promotion	Manufacturing	R&D	General adm. and overhead	Distribution	Others
Originator companies	21%	21%	18%	7%	1%	2%
Generic companies	13%	51%	7%	6%	3%	1%

Based on 32 originator companies and 16 generic companies.

Source: European Commission (2009a), Tables 4 and 7.

The main focus of this study in terms of innovation is on in-patent drugs, since this category represents the unique characteristics – and challenges – of innovation in the pharmaceuticals sector. Scherer (2007) observes, "[t]he discovery and development of new pharmaceutical substances are among the most interesting of innovation processes". This is not to remove generics totally from the scope of this study since they too have had a significant impact on innovation in the pharmaceuticals sector. In addition, statistics used in this study covering trade, production and R&D generally do not distinguish between in-patent drugs, generics and OTC drugs, and to this extent all these sub-categories are covered.

6. *See* Garnier (2008) for an illustration of the business model of large pharmaceutical companies. *See* Carpenter *et al*. (2009) for how regulatory process may actually work.

In addition, the pharmaceuticals sector as an industrial classification and a customs classification covers both intermediate and finished goods. Dosage-form pharmaceuticals, to be sold to consumers, are processed from pharmaceutical active ingredients (APIs), which are produced from the chemical intermediaries as inputs (US ITC, 2010). Trade and production statistics cover these items at the various stages of manufacturing.

3. The concept of innovation

OECD (2005, "Oslo Manual") defines an innovation as the implementation of a new or significantly improved product (good or services), or process, a new marketing method, or a new organisational method in business practices, workplace organisation or external relations. It is a continuous process that involves multiple aspects of firm activities. All innovations must contain a degree of novelty, which can be new to the firm, new to the market or new to the world (*ibid.*).

Among the four types of innovation (product innovation, process innovation, marketing innovation and organisational innovation (Oslo Manual)), much of the discussion in the context of this sector is about product innovation, since it is the cornerstone to bring about health benefits[7] and financial reward (Section II), although other types of innovation are also important to foster and materialise product innovation.[8]

It is noteworthy here that the levels of novelty attained by product innovation vary to a significant extent. A pioneer drug will establish a new therapeutic class with no substitutes in the market with patent protection, yet such "radical" innovation is more the exception than the rule.[9] Nevertheless, improvements in efficacy, reduction in adverse side effects, greater patient satisfaction, better compliance and cost effectiveness can offer significant value, and the cumulative benefits of such "incremental" innovation can make a more significant clinical contribution than the pioneer product (OECD, 2008b).[10]

7. *See* OECD (2008b, p. 53) for a survey of studies on health benefits of pharmaceutical innovation. However, a more recent study casts doubt on the robustness of the previous estimates comparing the benefits of old and new drugs (Law and Grépin, 2010).

8. For example, Achilladelis and Antonakis (2001, p. 537) explicitly excludes process innovations from its scope, since "they are hard to identify and evaluate with certainty" and "process innovations are seldom commercialized because companies seldom license their processes unless they license the corresponding product". Cockburn (2008, p. 225) argues "[w]hile product innovation remains the major focus of the industry, it is worth noting that process innovation capabilities may play an increasingly important role in the future", as generic suppliers compete on costs on one hand, and future biotech drugs will be very expensive to produce on the other.

9. One study estimates that only 10% of new chemical entities (NCEs) launched in 1975-2002 were both new chemical structures and delivered therapeutic improvements, and 56% were neither. (OECD (2008b) pp. 54-55)

10. Moreover, repurposing of existing drugs can prove to be a source of significant health benefit. *See* Andrew Jack, "Repurposing helps raise drug profits", *FT.com* (21 December 2010); *The Economist*, "Wonder drug: Aspirin continues to amaze" (9 December 2010).

4. Conventional industrial structure and its changes

Porter (1990) characterises the industrial structure of pharmaceuticals with (a) high entry barriers (the need for huge fixed research and development costs and economies of scale in selling to physicians), (b) slow development of substitutes, (c) low price sensitivity of buyers, (d) limited clout of suppliers (providing mostly commodities), (e) moderate rivalries which focuses on R&D rather than price, with patent protection slowing competitive imitation. This has supported the high profitability of the industry. In this conventional environment, the major source of competitive advantage has been differentiation by product innovation rather than cost leadership.[11]

This structure is undergoing substantial changes (Gassmann *et al.* 2008). First, contrary to the characterisation by Porter (1990) above, the development of substitutes is becoming faster. DiMasi and Paquette (2004) documents that the time between first-in-class approval and first follow-on approval in a class has been reduced at the rate of approximately 2-4 years per decade, or from eight years in the 1970s to less than two years in 1995-98 on average. This intensifies rivalries, including competition over prices, and can have a negative impact on company profits.[12] Past experiences in this sector show that second entrants can overtake the market share of the "first-in-class" with improved features and intensive marketing effort; i.e. the first-mover advantage for the pioneer product is considerable but not insurmountable (Berndt *et al.* 1996).[13]

This competition between in-patent drugs is in addition to competition from generics after patent expiration.[14] Generic drugs are taking an increasing market share in prescription medicine (KPMG International, 2009a), which has had an impact on market share and prices, although the share of generic medicines[15] and the patterns of evolution in prices and in market share vary significantly in different countries (Pammolli *et al.* 2002; Kanavos, 2008).[16] Moreover, the patents on many of the drugs launched in the 1990s are now expiring, which leads, in one estimate, to the loss of 2 to 40% of the revenue of the 10 largest pharmaceutical companies, and only four of them have R&D pipelines sufficiently valuable to offset these loses (PwC, 2008a; PwC, 2007a).

In addition to these factors, the rising cost of healthcare is an increasingly pressing issue in many developed countries, and cost containment initiatives has been taken including encouraging the use of generic drugs, demanding cost efficiency for use of drugs and putting pressures on drug prices (KMPG International, 2009; A.T. Kearney,

11. *See* Porter (1980, pp. 34-40) for cost leadership and differentiation as the two sources of competitive advantage.

12. Garnier (2008) illustrates "marketing wars" fuelled by shorter product monopolies.

13. *See* DiMasi and Paquette (2004) Table 1 for a list of "first-in-class" and second entrants.

14. Lichtenberg and Philipson (2002) argue that costs of competition between patented drugs are at least as important as generic competition.

15. Utilisation of generic medicines within the unprotected markets ranges from 89% in the US and 24% in Japan (IMS (2010) p. 3). *See* Iizuka and Kubo (2010) for an analysis of the generic market and the policy issues in Japan.

16. *See* Berndt and Aitken (2010) for a statistical account of recent acceleration of generic entry and the impact on prices in the United States.

2009a). Thus, the conventional conditions listed by Porter (1990) have been undergoing substantial transition,[17] and this is reflected in declining returns to shareholders.[18]

5. Innovation challenges and globalisation

To cope with these challenges, improvement in innovation performance is all the more important. The number of new drugs introduced in recent years, however, is not increasing, albeit not necessarily declining,[19] in spite of radical improvements in process technologies for drug discovery and rising R&D investment. Sales are now highly reliant on older drugs whose patent will expire sooner. Sales from products launched within the past five years accounted for only 7% of total sales (2.3% for large companies) in 2009.[20] On the other hand the cost of R&D to bring a new drug to market is increasing rapidly. Thus, Garnier (2008) declares "declining R&D productivity is at the center of (the industry's) malaise". (*See also* PwC, 2007a)

Pharmaceutical companies have pursued various initiatives, including large scale mergers, diversification through acquisitions of business areas such as generics, vaccines and consumer products, and alliances and smaller sized acquisitions to enhance patented drug portfolios (Ernst & Young, 2009, 2010a).[21] This paper focuses on one particular aspect: globalisation. As we shall see below, the global market has always been important for pharmaceutical companies, but it is also becoming important in the R&D process, and its scope is expanding with the entry of emerging economies. Before getting to those, the next section will further look at the nature of innovation in pharmaceuticals and current challenges.

17. European Commission (2009, p. 33) records the views of originator companies "that they are currently undergoing a phase of transition", quoting (a) difficulties in refilling the pipeline (in particular NCEs); (b) increasing safety and efficacy requirements for new medicines; (c) increasing control over prices and reimbursement levels, as well as on the prescribing practices by national health authorities; (d) patent expiration for a number of important blockbuster medicines; (e) new advances in genomics, proteomics and personalised medicines.

18. Garnier (2008); Cavalla and Minhas (2010) (PE ratios).

19. *See* Section II *infra* and Munos (2009) Figure 2 (for the performances of major pharmaceutical companies).

20. Andrew Jack, "Fall in R&D funding a blow for drug sector", *FT.com* (28 June 2010), citing CMR International's yearbook.

21. *See also* Andrew Jack, "Pharmas try different routes to survive", *FT.com* (12 March 2009); "Big pharma aims for reinvention" *FT.com* (12 May 2010); "Drugs groups diversify away from patents" *FT.com* (21 October 2010).

II. Innovation in the Pharmaceutical Sector

1. Historical development

Pharmaceutical innovation had its origin in the Chemical Revolution at the end of 18th century in France and medicinal discoveries made by physicians and academic researchers using experimental methods in chemistry during much of 19th century. Today, pharmaceutical innovation is a large industrial undertaking competing for the global market, with an increasing contribution from biosciences.[22]

The start of the modern pharmaceutical industry was marked by the entry of research conscious companies at the end of 19th century, especially German dyestuffs companies,[23] which developed and commercialised the medicinal discoveries. After the two world wars, the United States was both the largest market and the largest supplier, and competition among American firms resulted in intensive marketing, which was further accelerated with the globalisation of the market and the entry of European and Japanese firms. By the late 1970s, overseas sales by US firms exceeded 40% of their global sales (Figure 6[a]).

During the 1960s-70s various regulatory measures were introduced in many OECD countries. These included: clinical trials and approval processes for new medicines to minimise ineffective or harmful drugs; patent protection for pharmaceutical products in many European countries and Japan, as previously in the United States; and national healthcare systems and pricing policies in many European countries and Japan. With the heavy cost of discovery, development, approval and marketing of new drugs,[24] large companies established strong positions in the industry, although the differences in national regulatory regimes have had a significant impact on the development of the industry across countries.[25]

Limiting public expenditure on health care became a priority issue from the 1980s, and the use of less expensive generic drugs came to be advanced as one of the solutions.

22. This subsection draws heavily on Achilladelis and Antonakis (2001) pp. 573-584, 565. *See also* McKelvey *et al.* (2004) pp. 76-107; Scherer (2000) pp. 1306-16.

23. The origin of the modern pharmaceutical industry is attributed to the synthesis of aspirin by a chemist working for Bayer in 1897 (Santos, 2003, p. 694).

24. *See* Scherer (2007, pp. 19-20) for comparison of cost estimates since the 1950s and discussions on underlying regulatory developments. Regulation does not necessarily hinder innovation; Munos (2009) argues that a more demanding regulation in the United States and the United Kingdom has fostered a more innovative and competitive pharmaceutical industry. *See also* Scherer (2000) pp. 1313-14; McKelvey *et al.* (2004) p. 85; TAD/TC/WP(2010)9/FINAL, Section IV-3-ii).

25. McKelvey *et al*. (2004) pp. 80-88.

Due to strong innovation in the 1950s-70s, a number of effective generics and non-prescription drugs became available in the 1980s and the 1990s, after expiration of their patents, putting pressure on large pharmaceutical companies. During this period, however, "blockbuster" drugs gave a boost to the profitability of pharmaceutical companies.[26] They also divested non-pharmaceutical businesses and invested in M&As in the healthcare sector, including generic manufacturers and distributors.

On the other hand, the shift in the scientific basis of the industry from chemistry and pharmacology to the life sciences since the 1960s involved the introduction of new drug discovery methods and industrial application of biotechnology.[27] This pushed the industry into a process of transformation. Alongside the formation of very large vertically integrated global companies, small biotechnology firms have entered the picture founded with venture capital, and have formed alliances with established pharmaceutical companies.

2. Major players in pharmaceutical innovation

Most of the largest companies today have been in existence for 100 years, while having undergone a number of mergers and acquisitions.[28] These large companies have played a dominant role in product innovation. Munos (2009) shows that half of all the NMEs (new molecular entities) introduced since 1950 have been produced by 21 companies, all of whom are among the top 15 companies in Table 2 or a part of them (half of the 21 companies have since ceased to exist as an independent entity). The large pharmaceutical companies[29] accounted for around 75% of NMEs up until the early 1980s.

Despite the historically important role played by the large pharmaceutical companies and a series of mergers during the past decades, the level of market concentration has been relatively low compared with other R&D intensive industries,[30] and companies other than traditional large pharmaceutical companies (i.e. generic firms and dedicated biotech firms) are now ranked among the top 15 (Table 2; Grabowski and Kyle, 2008). Moreover,

26. Berndt (2001) shows that sales growth in the US prescription drug market in the 1990s was due to increased utilisation rather than price increase (Exhibit 1), in particular introduction of successful new drugs (Exhibit 4). Danzon and Pauly (2002) argue that the growth of prescription drug insurance coverage in the United States in the 1990s accounts for between one-quarter and one-half of the total growth in drug spending in 1987-96.

27. *See* e.g. Santos (2003), pp. 696-97.

28. For example, Pfizer (established in 1840) merged with Wyeth (1780) in 2009 and Pharmacia (1911) in 2003, both of which had previously undergone a series of mergers. Merck (1668) merged with Schering-Plough in 2009, the company formed from Schering (1851) and Plough (1908) in 1971. Novartis (1996) was established by a merger between Sandoz (1886) and Ciba-Geigy (1959), itself a merger of Ciba (1859) and Geigy (1758), (Achilladelis and Antonakis, 2001, pp. 558-59) Among over 4 300 companies that are engaged in drug innovation, only 32 have been in existence since 1950, including 23 smaller companies (Munos, 2009, p. 961).

29. "Large pharmaceutical companies" are defined as top 15 drug companies, or their predecessors and joint ventures.

30. The level of concentration is substantially higher at the therapeutic class level (Matraves, 1999, p. 174)

the share of NMEs introduced by large pharmaceutical companies has declined since the 1980s to less than 50% (Munos, 2009).

At the country level, the United States accounts for more than 40% of OECD expenditure on pharmaceuticals (OECD, 2008b), and it also remains dominant in terms of production and R&D expenditures. Among the 20 countries in Table 3, the top five countries account for 73% of production, 78% of value added and 88% of R&D expenditures. Apparently, there is no linear relationship between production level and R&D intensity; there are smaller and highly R&D intensive countries (e.g. Denmark, Czech Republic, Finland) alongside countries with larger production and lower R&D intensity (e.g. Italy, Korea, Ireland).[31]

Table 2. Largest pharmaceutical companies

1990 and 2009, sales in USD billions

1990	Company	Sales	Share	2009	Company	Sales	Share
1	MERCK	5.7	3.8%	1	PFIZER	57.0	7.6%
2	BRISTOL/SQUIBB	5.3	3.5%	2	MERCK & CO	39.0	5.2%
3	GLAXO	5.2	3.3%	3	NOVARTIS	38.5	5.1%
4	JOHNSON & JOHNSON	4.5	3.0%	4	SANOFI-AVENTIS	35.5	4.7%
5	SMITH KLINE BEECHAM	4.3	2.9%	5	GLAXOSMITHKLINE	35.0	4.7%
6	CIBA-GEIGY	4.2	2.8%	6	ASTRAZENECA	34.4	4.6%
7	AMERICAN HOME PRODUCTS	3.9	2.6%	7	ROCHE	32.8	4.4%
8	HOECHST	3.8	2.6%	8	JOHNSON & JOHNSON	26.8	3.6%
9	LILLY	3.7	2.5%	9	LILLY	20.3	2.7%
10	BAYER	3.3	2.2%	10	ABBOTT	19.8	2.6%
11	ROCHE	3.2	2.2%	11	TEVA	15.9	2.1%
12	PFIZER	3.2	2.2%	12	BAYER	15.7	2.1%
13	SANDOZ	3.2	2.2%	13	BOEHRINGER INGEL	15.3	2.0%
14	RHONE POULENC	3.2	2.1%	14	AMGEN	15.0	2.0%
15	UPJOHN	2.4	1.6%	15	TAKEDA	14.4	1.9%

Source: IMS Health (2010), *Top 15 Global Corporations, 2009, Total Audited Markets*; Achilladelis and Antonakis (2001), Table 9.

31. The production and value added by Mexico is similar levels to these countries (USD 18.4 and 9.5 billion , 2006), but its R&D expenditure is not available in the database. The latest figure of China's R&D expenditure is USD 0.7 billion in 2000, and no production data is available.

Table 3. Pharmaceutical production, R&D expenditure, value added (ISIC 2423, PPP, current prices, USD billions) and per capita pharmaceutical expenditure (USD, PPP)

Top 20 by R&D expenditure, 2006

	Production		R&D		R&D/Production		Value Added		Ph. Exp. p.c.
	2000	2006	2000	2006	2000	2006	2000	2006	2007
United States	115.0	178.5	12.8	38.9	11.1%	21.8%	55.0	91.5	876
Japan	46.6	62.6	4.8	9.4	10.3%	15.1%	21.6	25.4	548
United Kingdom	17.5	25.3	4.5	6.2	25.6%	24.4%	8.3	13.0	365
Germany	24.0	41.8	2.3	4.2	9.6%	10.2%	9.6	18.5	545
France	30.3	42.2	2.6	3.6	8.4%	8.5%	8.7	11.1	595
Switzerland	-	-	1.0	2.0[a]	-	-			
Belgium	7.0	10.5	0.7	1.1	9.4%	10.6%	2.8	4.1	562
Canada	6.0	8.9[b]	0.6	1.1	9.5%	12.5%	2.1	3.3[b]	665
Sweden	5.4	8.9	1.2	1.0	23.1%	10.9%	3.1	4.8	450
Spain	10.9	15.5	0.4	0.9	3.6%	6.1%	3.8	5.5	558
Denmark	0.3	5.1	-	0.9	-	17.8%	1.6	2.1	303
Netherlands	6.8	6.3	0.4	0.6	6.5%	9.8%	1.7	2.1	-
Korea	17.0	23.5	0.2	0.6	1.1%	2.6%	4.8	7.4	412
Italy	23.3	26.9	0.6	0.4	2.7%	1.5%	8.2	8.4	520
Hungary	2.4	4.3	0.2	0.4	6.6%	9.1%	1.1	2.1	434
Austria	2.6	3.1	-	0.3	-	10.3%	1.1	1.6	503
Czech Republic	1.1	2.1	0.03	0.3	2.9%	14.0%	0.5	0.7	348
Ireland	4.8	7.1	0.07	0.3[b]	1.4%	3.8%	2.3	2.4	595
Singapore	-	-	0.02	0.2	-	-			-
Finland	0.6	0.8	0.2	0.2	25.4%	28.5%	0.3	0.5	408

Note: R&D expenditures are distributed according to the main activity of the enterprise carrying out the R&D, except Belgium, Finland, France, Russia, Sweden and United Kingdom where data are distributed according to the product field of the R&D. There is a major break for the US data in 2003-04 (from USD 16 billion to USD 31 billion) due to a revision of the method used to classify data by industry. Figures expressed in national currencies are converted by PPP for GDP.

a: 2004, b: 2005

Source: OECD STAN Database for Structural Analysis, STAN R&D Expenditure in Industry (ISIC Rev. 3) ANBERD (Analytical Business Enterprise Research and Development) ed2009, OECD Health Statistics

3. Product innovation in pharmaceuticals

3.1 Pharmaceutical R&D

Product innovation in pharmaceuticals involves a uniquely long and costly R&D process, typically divided into discovery and development. Drug discovery includes basic science and research on disease physiology, identification and validation of disease targets in a body, identification and optimisation of drug candidates, and preclinical testing.

Development focuses on testing in humans, which typically proceeds in phases: small-scale trials to establish basic physiological data in healthy volunteers (Phase I), trials with subjects who have the targeted disease or condition to obtain evidence on safety and preliminary data on efficacy (Phase II), and large-scale trials to firmly establish efficacy and uncover side-effects (Phase III). If a drug candidate passes all phases, the results of these clinical tests will be compiled to support the applications for

marketing approval from the regulatory authority.[32] Further studies may be performed after marketing approval (Phase IV) to obtain approval for an additional medical condition for which the drug is to be used ("indication") or for marketing purposes.[33]

3.2 R&D and regulatory process

The process of R&D is closely interwoven with the regulatory process.[34] First, regulatory clearance is typically required to commence clinical testing.[35] After the three phases of clinical trials that follow, if it is believed that enough evidence is gathered to meet the regulatory requirements,[36] the sponsor can apply for marketing approval.[37] The approval process takes time, but the review time by the authority itself comprises only a small proportion compared with the time spent leading up to application for approval.[38] If the application is approved, the new drug can be placed on the market, but regulatory authorities typically monitor possible adverse effects of such drugs to update drug labelling and, on rare occasions, to re-evaluate the approval or marketing decision.[39]

Marketing approval is typically followed by a negotiation between the firm and a government body responsible for reimbursement and pricing, before actual marketing takes place. The time required for this phase is much less than that required for marketing approval, ranging in developed countries from a few months up to about 10 months.[40]

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32. This illustration is drawn on Cockburn (2008) p. 211 and CRA International (2008) p. 9; Lipsky and Sharp (2001); Berndt *et al*. (2006) pp. 95-98. More illustrations can be found in PhRMA (2010) p. 27; EFPIA (2009a) p. 6; EFPIA (2008) pp. 5-10.

33. Cockburn (2006) pp. 7-9. *See* Berndt (2001, pp. 109-10) for examples of post-launch research as marketing efforts.

34. *See generally* Lipsky and Sharp (2001); Lanjouw (2005) pp. 7-10.

35. E.g. Investigational New Drug (IND) application with the Food and Drug Administration (FDA) in the United States (exemption from marketing approval requirement to interstate transportation of drugs); Regulation within the EU is laid out in the Clinical Trials Directive (Directive 2001/20/EC).

36. The process of clinical trials involves close communication between the industry and the authority. *See* Berndt *et al*. (2006).

37. E.g. new drug application (NDA) with the FDA and an application. A marketing authorisation in the EU will be made with the European Medicines Agency (EMA) in the case of centralised procedure pursuant to Regulation (EC) No 726/2004, which applies to the treatment of AIDS, cancer, neurodegenerative disorders or diabetes.

38. *See* Berndt *et al*. (2006) p. 93. Furthermore, Berndt *et al.* (2005) shows that recent regulatory initiatives in the United States in 1992 onwards has significantly reduced the time required for approval, down from 33.6 months in 1979-1986 to 16.1 months in 1997-2002 on average.

39. *See* FDA website on Postmarketing Surveillance Programs; European Commission website on public health (Directive 2001/83/EC and Regulation (EC) No 726/2004). Recent examples are illustrated in *The Economist*, "Avandia survises, only just," *the Economist online* (15 July 2010).

40. Pharmaceutical Industry Competitiveness Task Force (2005) p. 41. EFPIA (2010) shows that the time between marketing authorisation and product access vary from 88 to 392 days in 15 European countries.

An initial patent application is typically made during the pre-clinical period.[41] Patent protection is effective for at least 20 years from the date of the filing under the TRIPS Agreement (Article 33). Assuming that it takes about 1.5 years before a patent is granted (Lanjouw, 2005), the effective patent life will be 18.5 years; moreover, the period of economic benefit from a patent will be further diminished due to delays associated with the regulatory approval process for new drugs prior to their market entry. Further delays may arise from pricing negotiations with reimbursement schemes and distributors. Many developed countries have legislated to partially restore the length of the full patent period, and similar legislation has been introduced in some developed countries. Overall, the typical new drug introduced in the United States during the mid-1990s had an average effective lifetime of approximately 12 years (Grabowski, 2002).

3.3 Costs of pharmaceutical R&D

Several studies have estimated the average cost of drug development, taking into account the probability of success and financial cost. An oft-cited study by DiMasi *et al.* (2003) estimates the total pre-approval cost per approved new drug to be USD 802 million (in 2000 dollars). They also find a 7.4% annual total cost increase between the 1980s and the 1990s, higher for clinical costs than for pre-clinical costs.[42]

Vernon *et al.* (2010) re-calculated the cost of capital used in DiMasi *et al.* (2003) and revised it upwards, resulting in the estimated total cost of USD 992 million. Further, DiMasi *et al.* (2006) focuses on the costs for biopharmaceuticals and estimated the number to be USD 1 241 million (in 2005 dollars), which is similar to the results in DiMasi (2003) considering the past growth rates in R&D costs. Adams and Brantner (2006) verified the results in DiMasi *et al.* (2003) based on an alternative dataset and arrived at a higher cost estimate (USD 868 million in 2000 dollars). A more recent study (Adams and Bratner, 2010) put the figure much higher at USD 1 214 million (in 1999 dollars).

Despite variations in these headline figures, they generally put the average cost of drug development to be around one billion dollars (or even more in current dollar terms) confirming a significant increase from comparable earlier estimates. Around half of the cost is actual out-of-pocket R&D expenditure and the rest are financial costs (i.e. reflecting the discount rate and the time spent). The costs for later phase clinical testing are generally much higher than those for earlier phases.[43] In addition, the cost and time involved vary significantly across therapeutic classes.

In the long process that spans discovery to launch (on average approximately 10-12 years), only one in approximately 5 000 to 10 000 investigational compounds ever makes it through the full development process to market launch (CRA International, 2008). Many of the compounds that reach the phase of clinical testing will be terminated due to

41. Cockburn (2008) refers to patent applications information as an indication of discovery activity.

42. Messinis (2004) points out that R&D price inflation is an important reason for apparent increase in R&D spending. Nonetheless, Cockburn (2006, p. 13) argues that even after adjusting for input cost inflation, R&D cost increase has been substantial.

43. Adams and Brantner (2010) is an exception to this, and they discuss the possibility that their method may be misallocating expenditure to drugs in different stages of development (p. 137).

concerns about efficacy and safety and also due to lack of promising commercial prospects (DiMasi, 2001).

4. R&D performance and its prospects

4.1 Current performance of pharmaceutical R&D

4.1.1 R&D spending and new drug entries

Cockburn (2006) argues that the rising costs per successful new drug constitutes the most worrying productivity statistic in pharmaceutical R&D. The estimates shown above are based on data up until the early 2000s, but more recent data do not appear to be any more encouraging. The growth of actual R&D expenditure by US-based companies was still increasing by around 10%, making up for about 17% of sales (Figure 1) (although there have been signs of reversal in the last couple of years).[44] Despite increasing R&D expenditures by pharmaceutical companies, the number of new drugs introduced to the market has not been increasing in recent years, neither in the United States (Table 4) nor in the European Union (CRA International, 2008).[45]

The number of potential new drugs in the R&D pipeline is indicative of the future trend in new drug entries, and the message is mixed. At the firm level, a majority of the top pharmaceutical companies saw growth in the size of R&D pipelines. The number of companies with active pipelines has also been continuously increasing for the past 10 years,[46] despite the unfavourable economic conditions in 2008-09.

Industry-wide figures (Table 5) show an upward trend in the size of the pipeline (CRA International, 2008, Figure 5),[47] but a rise in Phase II has not been matched by a rise in Phase III, suggesting that a number of potential drugs have been dropped in Phase II.[48] Although the figures at the pre-clinical stage appear less encouraging, they are more difficult to interpret.[49]

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44. The figures are not adjusted for inflation. Cockburn (2006, p. 28) cautions that PhRMA data does not cover R&D spending by non-US based companies, and the growth rate may be understated due to the absence of R&D by biotech companies in this series. More recent estimate suggests that the global R&D spending in 2009 declined by 0.3%. Andrew Jack, *supra* note 20. Morgan Stanley (2010) reports two cases of reduction in R&D expenditure in an effort to improve ROI for R&D.

45. The apparent decline in the number of approvals by the FDA since the mid-1990s has attracted attention, but Cockburn (2006, pp. 10-11) points out that the number of approvals in 1996 was exceptionally high, probably reflecting a regulatory reform to expedite FDA review process, and that apparent subsequent decline is a return to the historical norms. Munos (2009, p. 961) also concludes that the surge in 1996-97 can probably be ascribed to the clearing of the backlog of new drug applications.

46. Pharmaproject: *www.pharmaprojects.com/therapy_analysis/annual-review-2010-top-companies.htm*.

47. A sharp increase of the number of early stage pipeline products and more constant number of FDA approvals starting the late 1990s is also illustrated in Higgins and Rodriguez (2006) Fig.2. See also Ernst & Young (2010c) pp. 86-90.

48. Pammolli *et al*. (2010, Exhibit 1) documents a sharp increases of attrition rates at all phases of R&D, but especially at Phase II and Phase III. Munos (2009, p. 963) notes

The probability of failure in the R&D process is linked to the pipeline profile. Pammolli *et al.* (2010) argue that the reorientation of R&D investments toward projects with high risk and higher expected revenues from the 1990s to the 2000s explains most of the increased failure as well as the apparently lower success rates of R&D projects in the United States compared to European ones.

More generally, to properly evaluate R&D performance it takes much more than simple counts of new drugs that disregard the significant variation of the drugs' scientific significance, health impact and economic value (Cockburn, 2006).[50]

Table 4. NME drug and new biologic approvals by US Food and Drug Administration (FDA)

	2004	2005	2006	2007	2008	2009
New Molecular Entity (NME)	31	18	18	16	21	19
New Biologic License (NBL)	5	2	4	2	3	6
Total	36	20	22	18	24	25

Source: US FDA website, NME Drug and New Biologic Approvals, *www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/*

Table 5. The number of drug development projects

	2009	2010	Growth (2009/10)	Growth (1998/2007)*
Pre-clinital	5 063	4 855	-4.1%	2.1%
Clinical – Phase I	1 354	1 437	6.1%	7.9%
Clinical – Phase II	1 691	1 825	7.9%	7.3%
Clinical – Phase III	544	566	4.0%	1.5%

Source: Pharmaproject: *www.pharmaprojects.com/therapy_analysis/annual-review-2010-pipeline.htm*; *CRA International (2008), Figure 5.

4.1.2 Quality of new drugs and expected financial rewards of R&D

Studies have tried to evaluate new and future drugs from various aspects. Grabowski and Wang (2006) examined all new chemical entities (NCEs) first introduced worldwide in 1982-2003 and find that globally marketed NCEs (introduced in at least four of the G7 countries) are generally in an upward trend, and first NCEs introduction in a therapeutic class exhibits a moderate increase since 1993, while all NCE introductions peaked in 1985-88 in their dataset. The authors take these as an improvement of the quality of

that the probability that a molecule will successfully emerge from clinical trials is 11.5%, rather than 21.5% used in DiMasi *et al.* (2003).

49. Pharmaproject, *supra* note 46, notes that figures for pre-clinical stage are subject to changes in reporting practices by the industry and editorial practices by the drug database.

50. In addition to new drugs, Phase VI studies often bring about significant improvement in quality of approved drugs, in terms of improved formulations, delivery methods, and dosing protocols that do not involve new drug applications (Cockburn, 2006). *See also* Berndt (2001) pp. 109-10 for the benefits of post-launch research.

NCEs overtime. In contrast to this, a study based on academic assessments of European product approvals in 1995-2004 shows no apparent trend in either direction (CRA International, 2008).

The new drugs need to bring returns to match the increasing R&D costs to stay profitable in the long run. One study calculated the net present value (NPV) of the pipeline and finds that it has grown by 4% annually and R&D productivity has been essentially stable since 1999, although with a slight deterioration since 2006 (CRA International, 2008). More recent studies paint mixed pictures. David *et al.* (2009) estimates that the internal rate of return (IRR) on small-molecule (non-biological) R&D is about 7.5%, well below the IRR in 1997-2001 (about 12%), and below the current cost of capital (9.5%). In contrast, a study by Deloitte and Thomson Reuters estimate the IRR on future lifetime sales of each company's pipeline of late-stage drugs in test or submitted for regulatory approval to range from 8.4% to 18.4%. This return is greater than the weighted average cost of capital.[51]

4.2 Prospects for pharmaceutical R&D

We have thus far seen a continued increase in the number of potential new drugs in the earlier phases of clinical trials, a more moderate increase for Phase III, a stable flow of new drugs entering the market, and mixed evidence about possible improvement in the quality of new drugs, against the backdrop of ever increasing R&D expenditure. Taken together it appears that R&D productivity may well be declining in recent years.

Furthermore, the structural changes which the pharmaceutical industry is facing, such as increasing competition from generics, the looming patent expirations for drugs that represent a large portion of the current sales ("patent cliff"), a diminishing first-mover advantage and pressures on prices (*see* Section I), could leave a lasting impact on the future of product innovation, not just on the current profitability of the industry. Profitability, alongside a broad range of other factors,[52] is believed to be a strong determinant of R&D investment in pharmaceuticals by providing incentives and funding. Empirical evidence is generally consistent with this proposition (Box 1).

The pharmaceutical industry has thus been in the process of profound transformation. The next section will focus on how globalisation has been playing its part to face the current and future challenges.

51. Andrew Jack. "Drug groups' investments pay off", *FT.com* (30 November 2010); Deloitte, "Pharmaceutical R&D is healthy but needs to be fitter, according to new analysis from Deloitte and Thomson Reuters" (1 December 2010).

52. They include advancement in scientific knowledge, institutional and regulatory environment and market forces (OHE Consulting (2005) p. 6). These factors are inter-related since scientific advancement and regulatory changes can open new profit opportunities that induce companies to innovate.

Box 1. Profitability and R&D spending in the pharmaceutical industry: empirical studies

Two distinct channels through which profitability affects R&D spending[53] have been proposed: first, current profits serve as a source of R&D funding,[54] and second, expectations of future profit opportunities by current market conditions can have an influence on R&D investment (Scherer, 2001). Scherer (2001, 2007) compares the patterns of deviation from the trend for gross margins and R&D expenditures and found that when margins rise relative to trend, R&D rises in near tandem. He suggests a scenario in which new science-based opportunities create profit potentials, and companies that recognise these compete vigorously to exploit the opportunity, and in the process dissipate most or all of the available rents ("competitive rent seeking").[55]

Achilladelis and Antonakis (2001) tests how recent cash flow variables (sales and profit) and R&D expenditure (both with lag) explains the current level of R&D expenditure for individual pharmaceutical companies for 1950-1989 and find strong linkages between these variables and R&D expenditure. Grabowski and Vernon (2000) studied pooled data of 11 major drug firms in 1974-94 and find that industry wide expected returns (measures of R&D productivity and industry margins) and firm level cash flows (with one year lag) are important explanatory variables of R&D intensity. Building on this, Vernon (2005) used firm level financial data for 14 major pharmaceutical firms in 1994-97 and shows similar results.

Acemoglu and Linn (2004) took a different approach to investigate the effects of profit incentive on innovation. They used US demographic changes as an exogenous variable that drives market size and find that a 1% increase in potential market size leads to a 4% increase in the entry of new non-generic drugs and to a 4-6% increase in the entry of new molecular entities.[56]

More closely linked to policy issues, Giaccotto *et al.* (2005) investigates the impact of drug prices on industry-level R&D intensity in the United States in 1952-2001 and find that a 10% increase in the growth of real drug prices is associated with a 5.8% increase in the growth of R&D intensity. Cook *et al.* (2010) examined the impact of the increasing rate of generic utilisation on drug prices in the United States in 1992-2008 and find that a 10% increase in the generic utilisation rate implies a 1.5% decrease in real drug prices. Taken together, they argue that price control and increasing generic drug unitisation both have a negative impact on R&D activities by pharmaceutical companies. In addition, to the extent that the length of drug review times by the regulatory authority affect expected returns to R&D investment, shorter review times can increase R&D spending, as Vernon *et al.* (2009) find based on seven large US-based drug companies in 1990-99.

Other studies that looked into non-US markets, including Golec and Vernon (2006)[57] (comparing the US and EU markets in terms of R&D spending, price levels and profitability) and Mahlich and Roediger-Schluga (2006) (on Japanese firms) [58], similarly show linkages between current profitability and R&D.

53. Scherer (2007) adds that the causation cannot be in reverse, since R&D expenditure cannot immediately affect profitability given the long process of drug development.

54. Scherer (2001) notes "[f]or most well-established corporation, R&D spending is not greatly dependent upon internal cash flow, but small high-tech enterprises […] and the research intensive pharmaceutical industry were probable exceptions."

55. *See also* Giaccotto *et al*. (2005, p. 200) ("firm managers in the pharmaceutical industry employ the R&D-to-sales ratio when making a future year's budgeting decisions").

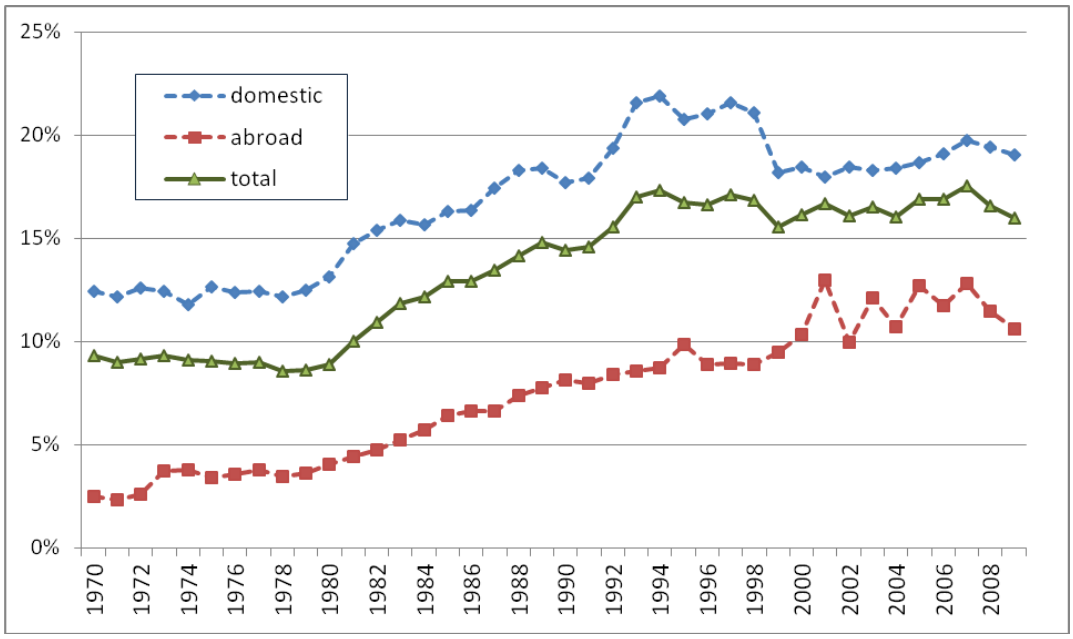
56. These NMEs contain active ingredients that have not been previously marketed in the United States, representing more radical innovations than other non-generics (there are 442 NMEs and 2 203 new non-generics in their dataset).

57. Based on the fact that overall drug prices have risen more in the United States than in the European Union, and US firms have been more profitable and more R&D intensive than EU firms, they show, using financial data in 1993-2004, the more sensitive a firm's sales are to the US (EU) price index, the greater (smaller) its R&D spending.

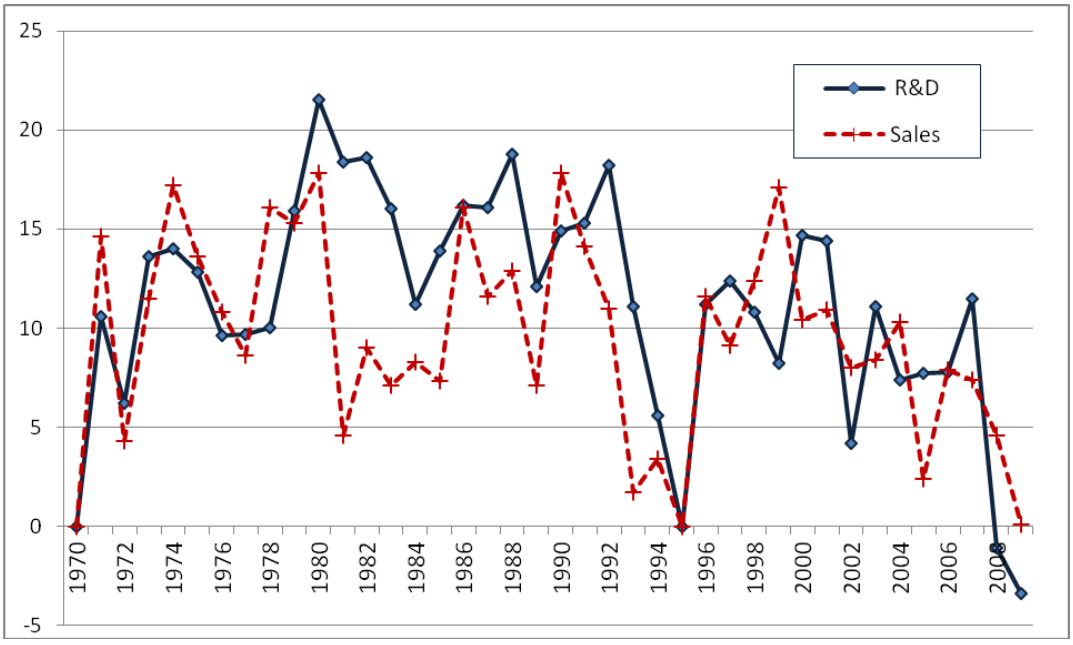
58. Relying on the same method as Grabowski and Vernon (2000) and data from 15 major Japanese pharmaceutical firms in 1987-98, they reached similar results, albeit with much smaller coefficients, due perhaps to regular price cuts in pharmaceuticals in Japan (pp. 151, 161). They further found that, by refining the estimation method, cash flow is

Figure 1. Evolution of R&D spending by US based pharmaceutical companies

(a) R&D/sales ratio



(b) Annual % change (domestic and abroad)



Source: PhRMA (2010), Table 1.

no longer statistically significant (industry profit margin remains statistically significant), casting doubt on the previous study.

III. Pharmaceuticals in the Global Market

1. Global trade in pharmaceuticals and innovation

1.1 Global trade in pharmaceuticals, 1995-2009

World trade in the pharmaceuticals sector (defined as HS Chapter 30 and headings 2936, 2937, 2939 and 2941 in this sub-Section)[59] grew by almost six times in 1995-2008, or at about 15% annualised growth (Figure 2[a]). Throughout this period, around 80% of world trade has been taking place between high-income countries (HICs), with most of the rest being exports from high income countries to low- and middle-income countries (LMICs), suggesting that the growth rates have been substantially similar across different income groups.[60] However, an early sign of a shift in the market opportunities may be detected in a gradual increase in the share of the exports from the HICs to the LMICs and corresponding retreat in the share of exports between the HICs.

Classified by end use of goods according to the Broad Economic Categories (BEC) (United Nations, 2002), "consumer goods" (HS 3003-3005)[61] account for three quarters

59. The trade data is taken from UN Comtrade based on HS1992, supplemented by HS1996 data. The coverage is in reference to the coverage of sectoral tariff elimination agreed in the course of the Uruguay Round (*see* GATT, Trade in Pharmaceutical Products, L/7430 (25 March 1994)). However, the agreed coverage includes exceptions to headings 2936, 2937, 2939 and 2941, and additions based on INN (international non-proprietary number) from the World Health Organization (WHO), prefixes and suffixes and product names listed in the GATT document above (L/7430), which has since been further expanded. However, these exceptions and additions are not defined by HS headings, therefore systematic trade data is not available, and this further makes it unfeasible to precisely assess the impact of the successive additions of products (*see* US ITC (2010) 3-2). In addition, successive amendments to the HS classification since then have also affected the coverage of these headings, albeit to a limited extent.

60. Income group classification is in accordance with World Bank income classification (August 2010). Chinese Taipei is categorised as high income for the purpose of this section (*see* World Bank, *How we Classify Countries*, *http://data.worldbank.org/about/country-classifications*).

61. Not all products under HS3003-05 are immediately sold to the consumers. In particular, items under HS3003 are "not put up in measured doses or in forms or packings for retail sale". Olcay and Laing (2005, p. 23) refers HS3003 as APIs. In contrast, US ITC (2010) explains "[d]osage-form pharmaceuticals are classified in [HS] chapter 30. […] Most of the bulk pharmaceuticals [APIs] and chemical intermediates are organic chemicals classified in chapter 29".

of the world trade, whereas the rest being "intermediate goods" (Figure 2[b]).[62] The share of "consumer goods" in the world trade in this sector has followed an upward trend between the mid-1990s to the mid-2000s, despite the increasingly prevalent outsourcing of manufacturing in recent years.

Most of the top exporters are OECD members, but emerging economies such as China and India are now among the top 20 (Figure 3[a]). Most of these leading exporters recorded double digit growth especially in the 2000s (except Japan). More than 70% of the exports to HICs are finished goods for most of these major exporters; more variation can be seen for the exports to LMICs but finished goods occupy more than half of such exports (Figure 3[b]). A major exception is China, over 70% of whose exports are intermediate goods. The weight of LMICs as export destination varies across countries; the shares of exports to LMICs are higher in France and Switzerland (especially for consumer goods), but much lower in Ireland, exporting mainly to the EU market. Trade with LMICs is more important for China and India.

Major importers are also OECD members, but emerging economies are among the top 20. All top 20 importers recorded double-digit growth in 2001-09 (Figure 4). Imports from China and India are gaining weight in most of the income categories for both types of goods (consumer goods and intermediate goods) (Figure 5). In particular, almost one third of the imports in consumer goods by low-income countries are from India, over one fifth of the imports in intermediate goods by lower-middle-income countries (including India) are from China and over one–eighth of such imports by low-income countries are from India. In contrast, their shares in imports by HICs in consumer goods remain much smaller. While HICs are the largest export destinations in value for China and India, LMICs are their growing market.

The trade data shows that India is more specialised in final goods sales to developing countries, whereas China is more oriented to supplying intermediate goods for developed countries. This reflects the features of the industry in the two countries: China has traditionally focused on basic intermediaries and the active pharmaceutical ingredients (APIs) with smaller presence in the finished drugs (PwC, 2008b). India has become best known as the supplier of generics, accounting for 20% of the global generics market (compared to 4% in 2005),[63] although contract manufacturing in APIs is another strong segment for Indian firms, boasting over 100 US FDA-certified manufacturing sites,[64] more than in any country except the United States (PwC, 2010b).

WTO (2005) attributed the source of the expansion of pharmaceuticals trade to a) the strong demand in the major markets, b) a concentration of production as a result of M&As and outsourcing, c) trade liberalisation since 1995, d) the growth of Ireland due to substantial foreign direct investment (FDI) inflow, e) the establishment of Belgium's role as a hub for the distribution of pharmaceuticals since 2001, and f) a rise in parallel imports due to price differences, especially in the European market. While some of these

62. These HS headings are not an exhaustive list of pharmaceutical intermediate goods. Other items that belong to other headings in chapter 29 may be used to produce pharmaceuticals, which may still be covered by the UR pharmaceutical arrangement (*see supra* note 59).

63. Mani (2006) p. 10.

64. All domestic producers are obliged to comply with India's Good Manufacturing Practice (GMP), but it is less stringent than than that of the US or the WHO (Gehl Sampath (2007) pp. 19-20).

factors only explain one-off acceleration, the growth path was sustained into the latter half of the 2000s.[65] There will be more uncertainties in coming years especially in the major markets, due to the pace of economic recovery, pressures on healthcare spending and patent expirations and entry of lower-cost generic alternatives, and the major driver of growth is anticipated to shift to the emerging markets.[66]

1.2 Global market opportunities and R&D

Global market opportunities that extend beyond national borders have been an essential part of pharmaceutical companies as sources of revenue, which in turn has provided incentives and funding for further R&D investment (Section II). For US-based Pharmaceutical Research and Manufacturers of America (PhRMA) member companies, the share of sales abroad climbed beyond 40% in the late 1970s and since remained between 30-40% (Figure 6[a]). Foreign market sales have been even more important for pharmaceutical companies originating in smaller countries (Scherer, 2000; Gassmann and Reepmeyer, 2005). The industry's strong acceleration in growth, increased profitability, higher R&D intensity and major new drug introductions since the 1980s (Achilladelis and Antonakis, 2001; Grabowski and Vernon 2000, Table 1, Figures 2 and 5) was a consequence of global sales.

Globalisation of the market can also be seen in the geographical reach of a product. Lanjouw (2005) shows that most of the countries studied (including non-OECD countries) had access to over 70% of blockbuster drugs[67] launched in 1982-92 (91 NCEs) within 10 years after the launch, albeit with varying time lags.[68] The author further notes that there was a marked increase in the number of countries that new drugs reached within a short span after their global launch since 1995. To echo this point, Grabowski and Wang (2006) shows that 42% of 919 NCEs introduced world-wide in 1982-2003 are introduced in at least four of the G7 countries, and such "global" NCEs has been on an upward trend during the period.

The particular importance of success in the global market in this sector is accentuated by the highly skewed distribution of financial rewards to a limited number of globally successful drugs. Grabowski *et al.* (2002) shows that the top decile of NCEs (ranked by their individual present values of returns) accounts for half of the total present value generated by all 118 NCEs introduced into the US market in 1990-94. Moreover, only the top three deciles of drugs have estimated present values exceeding average R&D costs.[69]

65. OECD (2008b, p. 41) notes that parallel trade is greatest within the EU, and it was estimated to account for about 2% of the total pharmaceutical market in 2003, but growing fact.

66. IMS Health (2010), Press Releases: IMS Forecasts Global Pharmaceutical Market Growth of 5-8% Annually through 2014; Maintains Expectations of 4-6% Growth in 2010 (20 April 2010).

67. "Blockbusters" are defined in this study as those that were found among the top 200 in terms of world revenue in 1998 or 2003, or among the top 100 US revenue earners in 1993 or 1995 (Lanjouw (2005), Table 1).

68. Lanjouw (2005, p. 15) shows that wider range of new drugs launched in 1982-88 (300 NCEs) eventually reached 20 countries on average. 54 were marketed in just a single country, 23 being in Japan and 13 being in Italy.

69. *See also* David *et al.* (2009).

Skewed distribution of financial reward can also be seen at the company level, as many large pharmaceutical companies rely on top selling products for a significant proportion of their revenues (Table 6).[70] This implies that current R&D investment is also highly reliant on the revenues generated by these globally successful products for funding.

Beyond the role of exports as an essential contributor to sales and profits, some studies have more specifically looked at the impact of foreign sales on R&D activities. Giaccotto *et al.* (2005, Table 1) presents an estimate that a 10% increase in the growth of foreign sales share (as a percentage of total sales) is associated with a 1.7% increase in the growth of R&D intensity. Matraves (1999) argues that increasing R&D intensity (as a percentage of gross output) in Japan in 1983-92 can be explained by globalisation, which opened up new geographical markets to Japanese firms, and also led to more competition in the Japanese market. This has raised the incentive to escalate R&D in order to capture a larger global market share. A statistical analysis at the country level in the Annex to this paper provides further support to this proposition (Box 2).

Table 6. Top selling prescription medicines, their global turnover and the shares in company turnover

Company	Product name (INN)	Therapeutic class	Global turnover, share (million euros)
Pfizer	Lipitor (atorvastatin calcium)	cardiovascular system	9 252 (30%)
Glaxo Smith Kline	Seretide/Advair (fluticasone + salmeterol)	respiratory system	5 109 (18%)
Sanofi-Aventis	Clopidogrel (clopidogrel)	blood and blood forming organs	2 424 (9%)
Hoffmann-La Roche	Herceptin (trastuzumab)	antineoplastic and immunomodulating agents	2 954 (13%)
Nycomed	Pantoprazole (pantoprazole)	alimentary tract and metabolism	1 685 (55%)
Wyeth	Enbrel (etanercept)	antineoplastic and immunomodulating agents	1 492 (13%)
Eli Lilly	Zyprexa (olanzapine)	Nervous system	3 474 (27%)
Novartis	Glivec (imatinib)	antineoplastic and immunomodulating agents	2 228 (13%)
Johnson & Johnson	Risperdal (risperidone)	nervous system	3 318 (18%)
Amgen	Aranesp (darbepoetin alfa)	blood and blood forming organs	2 637 (25%)
Total/Average			34 574 (19%)

Note: Ranked by EU27 turnover.

Source: European Commission (2009a), p.29.

70. Attridge (2008, p. 13) claims that for leading companies at any given point in time 70-80% of total revenue comes from no more than three to five patented products.

Box 2. Exports, intellectual property, domestic market and R&D activities

As background work to this paper an external consultant carried out an empirical investigation of the determinants of R&D activities in the pharmaceuticals sector, including various measures of trade. The author first identifies a number of variables that are potentially linked to R&D intensity (those on the left in the diagram below). These variables are combined into new variables ("principal components") which are then used to explain the pattern of R&D intensity across countries.

He uses five principal components, three of which are significantly correlated to R&D intensity, in particular the first component (heavily influenced ["loaded"] by variables relating to scale of exports, export specialisation, intra-industry trade, domestic pharmaceutical expenditures per capita and royalty income) and the fifth component (geographical concentration of export destination and royalty income). The author interprets this result as evidence that supports a positive influence of exports on innovation by way of financing the R&D.

There is a scarcity of empirical studies that directly tests the linkage between export performance and R&D spending, and this exercise is one contribution to fill the gap.

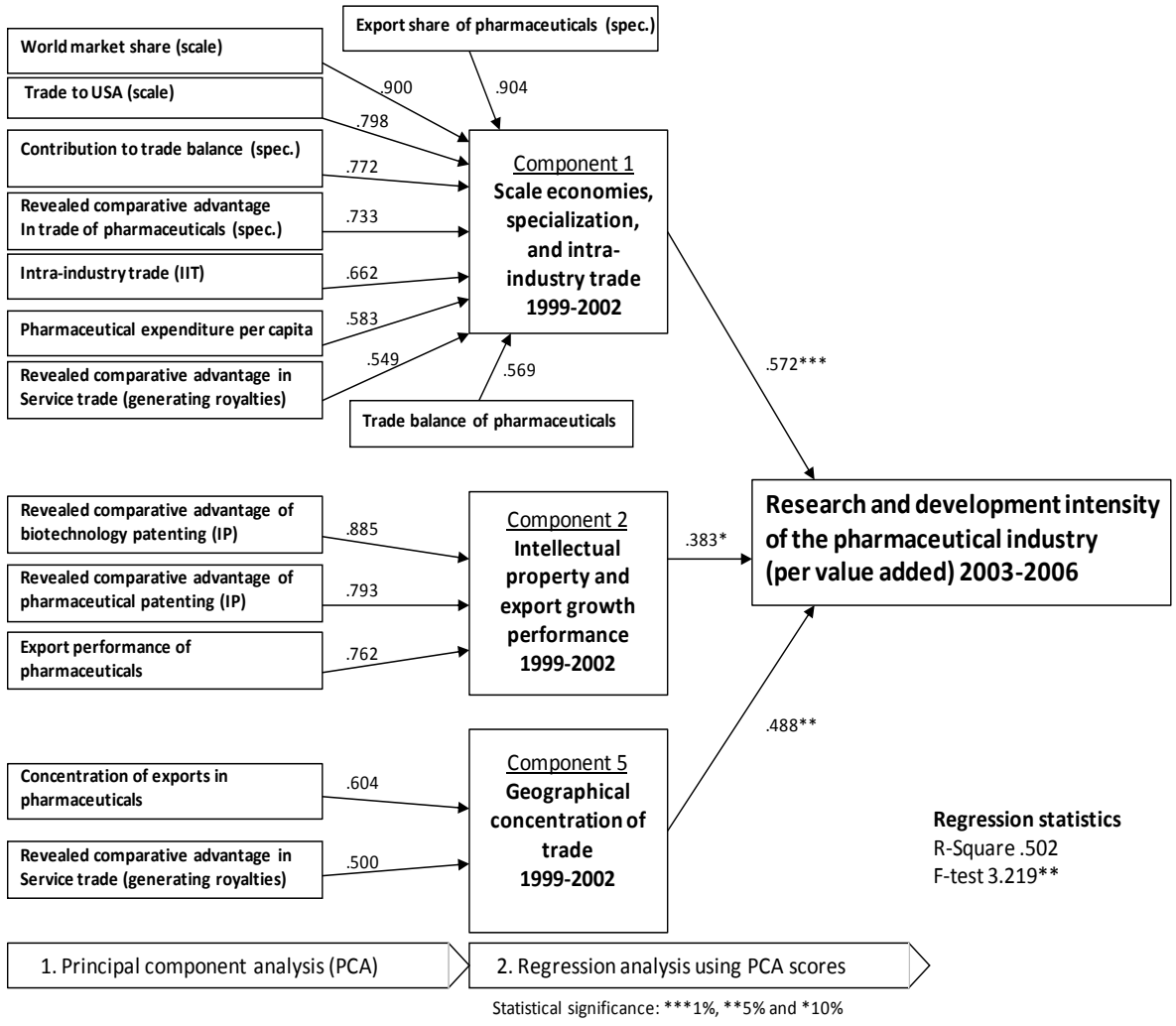


Figure. Trade patterns (Component 1), Intellectual property (Component 2), and Geographical concentration of trade (Component 5) precede innovative activity (R&D intensity) within 22 OECD countries.

Source: Raine Hermans, "Trade and Innovation in Pharmaceuticals", available on request from the Secretariat.

1.3 Health benefits of pharmaceuticals imports

Generally, one of the key linkages between trade and innovation is diffusion of technology as embodied in traded products (e.g. OECD, 2008a). In the pharmaceuticals sector in particular, global sales of pharmaceutical products represent global diffusion of medical technology generated as a result of highly intensive R&D efforts in the exporting countries, with importing countries receiving the benefits of the results of R&D in terms of health improvements, even without engaging in R&D activities themselves. This is the thrust of Papageogiou *et al.* (2007), which argues that "medical innovation diffuses steadily across the world contributing to significant improvements in life expectancy." They identified two distinct channels of such diffusion: imports of medical goods (e.g. drugs, vaccines and medical equipment) and the direct flows of medical knowledge from a few "frontier countries" (the United States, Europe and Japan) to the rest of the world, a flow facilitated by information networks created by medical students from non-frontier countries who study in frontier countries. They estimate that the expected difference in life expectancy between countries at the 25th percentile and the 75th percentile in terms of medical imports per capita would be about 3.5 years, holding other variables constant.[71]

The health improvement itself is a valuable outcome of trade in pharmaceuticals, but it can also have a long term effect on economic development. Cervellati and Sunde (2005) present a formal model based on the idea that longevity positively affects human capital formation since higher life expectancy provides incentives for individuals to get educated. The human capital formation further induces the longevity of future generation and technological progress, leading to "a potentially virtuous circle of more human capital formation, higher life expectancy, and faster growth". They argue "[e]conomic improvements and improvements in life expectancy are miniscule and almost undetectable for a very long period. But these improvements eventually lead to the disappearance of the stagnant regime and trigger a rapid transition toward sustained growth and improved living conditions."[72]

Researchers in biological sciences have recently analysed the biological linkage between health status and improvement in human capital, focusing on "the parasite stress". Eppig *et al.* (2010) argue that since human newborns demand disproportionately higher energy for their brains (87% of the body's metabolic budget; 34% at age ten), "[p]resumably, if an individual cannot meet these energetic demands while the brain is growing and developing, the brain's growth and developmental stability will suffer." Parasitic infection affects such development by taking the energy away from the hosts to feed or reproduce themselves, by limiting the host's intake of nutrients by causing diarrhoea, or by activating immune system of the host to fight off the infection at the expense of the host's energy. They test this "parasite-stress hypothesis" to explain the worldwide distribution of intelligence, and find that "infectious disease is a significant predictor of average national intelligence quotient (IQ) scores", while "education and GDP per capita are not statistically significant when other factors are controlled for".

71. Their results also show that income levels, which are often considered as a determinant of health status, do not actually have an explanatory power, after controlling for other factors.

72. *See* Castelléo-Climent and Doménech (2008) for empirical evidence about the linkage between life expectancy and human capital accumulation.

While there are a number of possible determinants and impediments to economic growth,[73] a full survey of literature is beyond the scope of this paper. Yet these studies suggest that health status can be an important contributor to future innovation and economic growth, and that trade in pharmaceuticals can play a role in facilitating it.

1.4 Shifting market opportunities

The major part of the pharmaceutical market has been occupied by the developed countries, but the emerging economies are rapidly gaining ground. In 2009, North America, Europe and Japan respectively accounted for 40%, 31% and 11% of the global market. Whereas these mature markets grew by 5-8% in 2008-09, other areas such as Asia and Latin America recorded double digit growth rates.[74] Focusing on seven emerging markets,[75] Anderson et al. (2009, Figure 3) shows that the market size could almost double by 2013. They together generated one third of global sales growth in 2009, matching the size of combined sales growth generated in the United States, Canada, EU5[76] and Japan (*ibid.* Figure 4). China is expected to take over Germany to become the third largest market in 2010, after the United States and Japan.[77] India is expected to be one of the top 10 markets by 2020. (PwC, 2010a)

The growth in the demand for pharmaceutical products in these markets reflects their economic growth and the rising number of middle-class. Moreover, health care reforms to improve access to drugs and health care services are underway in many of these countries, and protection of intellectual property has been improved in compliance with the TRIPS Agreement (Anderson *et al*. 2009; Ernst & Young, 2010b).[78] In the case of India, for example, the lack of product patent since 1972 meant very little incentive for the global pharmaceutical companies to introduce new drugs in Indian market (Prahalathan and Baruah, 2007), but the situation has fundamentally changed.

Recent quarterly results of multinational pharmaceutical companies show that emerging markets are increasingly important sources of revenue. However, penetrating these non-traditional markets poses a challenge for pharmaceutical companies. First, emerging markets are different from mature markets in many respects; besides the difference in the levels of income, the infrastructure for sales and marketing are much less established, and the proportion of out-of-pocket spending on pharmaceutical sales are

73. Earlier economic literature argued that income is the most important determinant of health status, but this does not fit well with historical development in many countries (Cutler *et al.,* 2006, pp. 110-11); *see also* Papageorgiou et al. (2007, p. 410). Eppig *et al*. (2010) reviews the studies that proposed alternative explanations about average national IQ score. *See also* Easterly (2002) for illustrations of how various possible determinants of economic growth have worked in practice.

74. IMS Health, "Total Unaudited and Audited Global Pharmaceutical Market By Region", cited from *IMS Health Market Prognosis*, March 2010.

75. Brazil, China, India, Korea, Mexico, Russia and Turkey.

76. France, Germany, Italy, Spain and the United Kingdom.

77. IMS Health Press Release, *IMS Health Forecasts Global Pharmaceutical Market Growht of 5-7 Percent in 2011, Reaching $880 Billion* (6 October 2010); Andrew Jack, "China to be top three prescription drug market", *FT.com* (7 October 2010).

78. Abeer Allam, "Saudi changes attract drug companies", *FT.com* (6 December 2010) (for an example of Saudi Arabia).

much higher in these countries (Anderson *et al*. 2009). Second, in devising an entry strategy to emerging markets, diversity amongst them cannot be overlooked. The income levels and healthcare coverage are very different within this group. Their health profiles are also diverse; they suffer from different types of diseases and take different kinds of drugs, reflecting heterogeneity in ethnic origins, diet, environmental factors, demographics and healthcare systems and other policy variables (Anderson *et al.* 2009; PwC, 2007a).

Expanding the access to new patients in emerging markets demands creativity and local knowledge (Ernst & Young, 2010b). Multinational companies have pursued various strategies,[79] including partnership with local players to improve the chances of and gains from success.[80] One of these is differential pricing, setting the prices at much lower levels, in order to overcome the greater price sensitivity in these markets.[81] In the case of the Indian market, several of the global companies are entering into OTC market, which can help them to seize significant market potential and to build brand awareness among the consumers. Penetrating into rural market is a major challenge for these companies without large field sales forces that large Indian companies have. Establishing partnership with the local companies can be one option, and some companies are reportedly targeting post office to sell OTC drugs (PwC, 2010a).

Moreover, the emerging markets can be an important source of product innovation, which leads to radically lower cost and higher efficiency both for local needs and global use. The emerging markets are not just low cost locations in the R&D process, but they can also be a source of innovative ideas (A.T. Kearney, 2009b).[82]

Beyond exports to these markets, interest in M&As involving emerging countries has been growing; typical motivations include sales and marketing, distribution as well as R&D (PwC, 2008b). Out of 305 deals within the Central Asia/Asia-Pacific region from mid-2008 to mid-2009, China and India accounted respectively for 146 and 38 deals (KPMG International, 2009b). For example, Novartis reached an agreement to acquire an 85% stake in the Chinese vaccines company Zhejiang Tianyuan Bio-Pharmaceutical Co., Ltd as part of a strategic initiative to expand their presence in both China and vaccines. Daiichi Sankyo acquired Ranbaxy Laboratories Ltd. of India in 2009, which gave it an opportunity to enter into the generics market and also India and other emerging markets.[83]

79. On the complexity of the market and various strategies taken by multinational pharmaceutical companies, *see e.g.* Mina Kimes, "Big Pharma's Challenge: Figuring out China", *CNNMoney.com*); Andrew Jack, "Big pharma's Brazilian prescription", *FT.com* (14 November 2010).

80. *See* Ernst & Young (2010) p. 28 (based on business experiences in China and India). *See also* Takechi (2010) (based on a statistical analysis on Japanese antibiotics market).

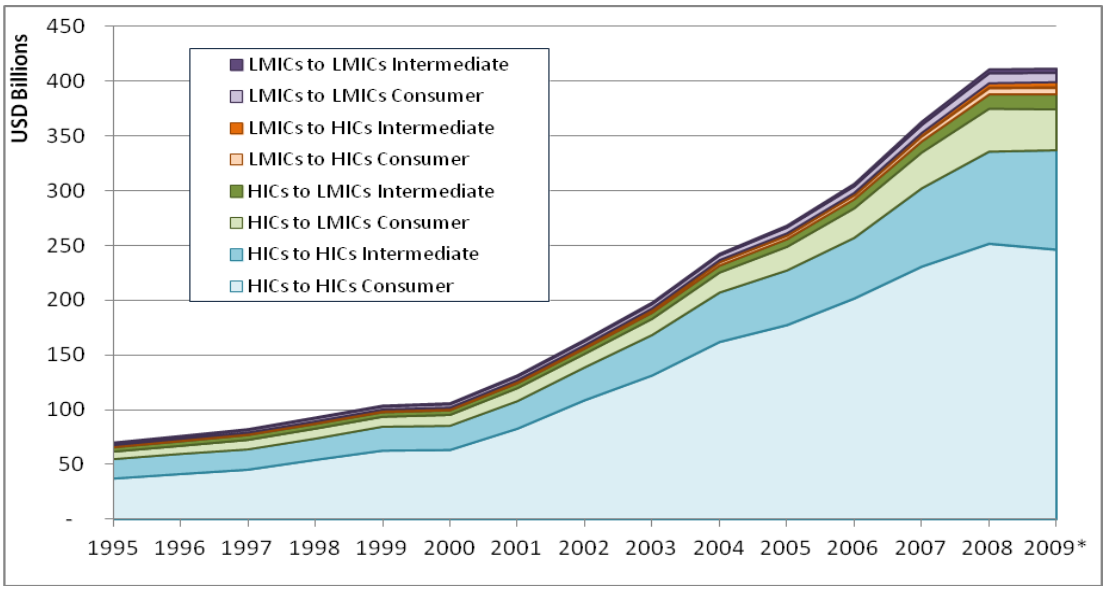
81. For example, GalaxoSmithKline (GSK) has been experimenting tiered pricing in which differential prices are introduced within markets to reach new customer base, aiming at increase in the volume of sales. See GSK Corporate Responsibility Reports 2008 and 2009; PwC (2009) p. 19. Merck & Co. has launched differential pricing through its anti-diabetic drug in India (PwC, 2010b, p. 5).

82. *See also* [TAD/TC/WP(2010)0/FINAL], Section III. 2. iii) (consumer chemicals); Stefan Wagtyl (2011), "Indian R&D unhindered by cost issue", *FT.com* (a new camera for X-ray machines).

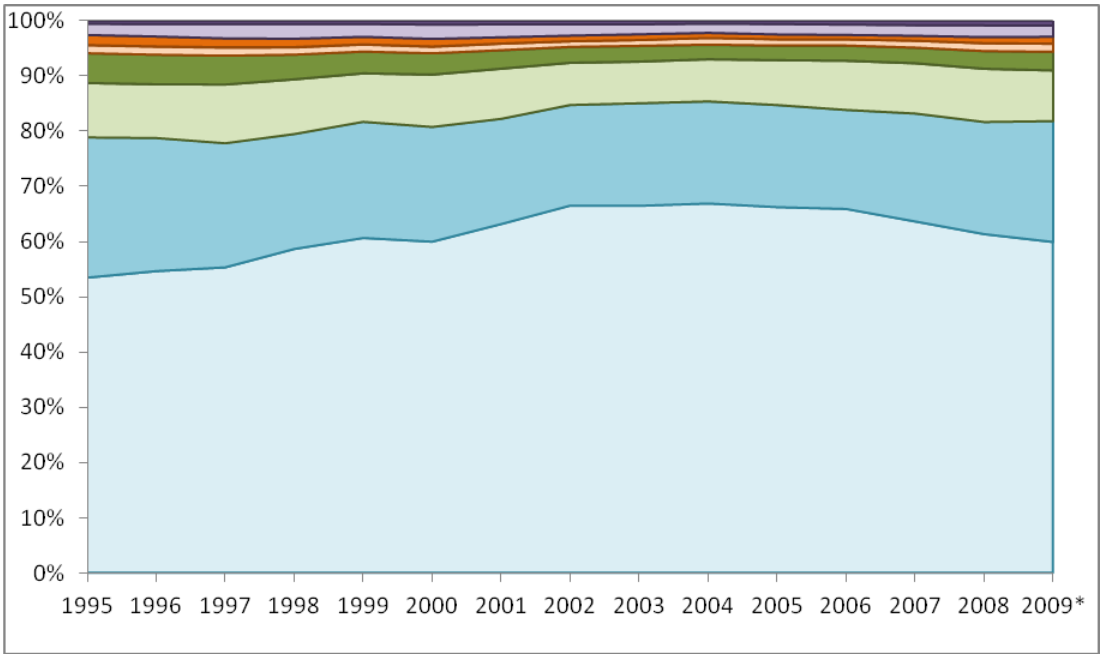
83. More recent examples include the acquisition of Paras Pharmaceuticals (India) by Reckitt Benckiser (UK) and of Guangdong Techpool Bio-Pharma (China) by Nycomed

Figure 2. Exports in pharmaceuticals

(a) export value



(b) % share



Note: HIC: high-income countries, LMIC: low- and middle-income countries

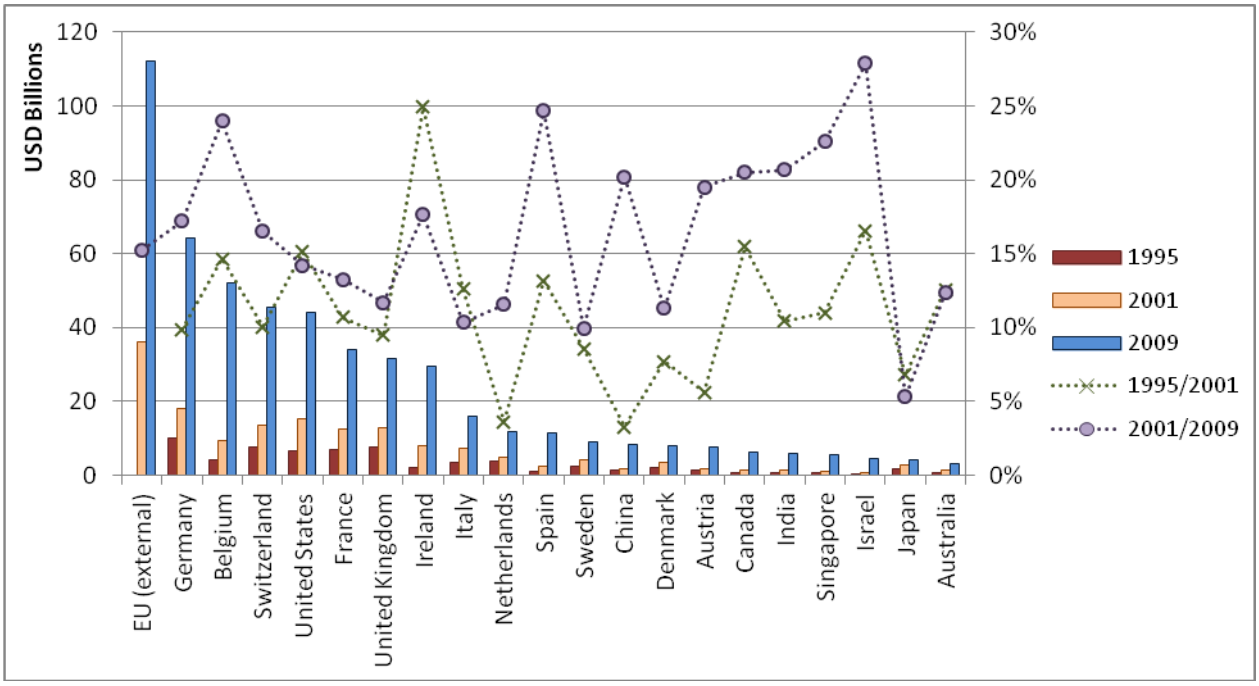
Figures in 2009 are still missing in the database for some major exporters at the time of compiling the trade data (e.g. Spain [USD 11 billion in 2008]).

Source: UN Comtrade

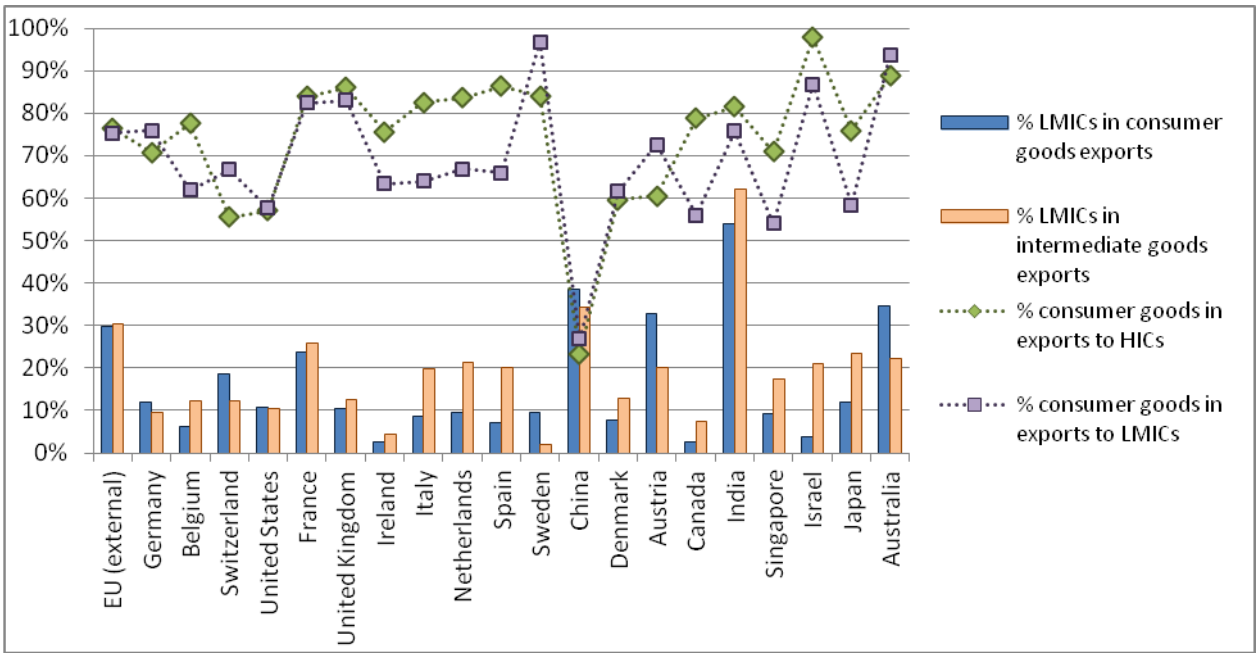
(Switzerland). *See* James Fontanella-Khan and Louise Lucas, "Reckitt wins tussle for India's Paras", *FT.com* (13 December 2010); Andrew Jack, "Nycomed to take control of China drugs group", *FT.com* (1 November 2010).

Figure 3. Major exporters

(a) export values in 1995, 2001 and 2009, and growth rates



(b) % share by type of goods (consumer, intermediate) and income group in 2009

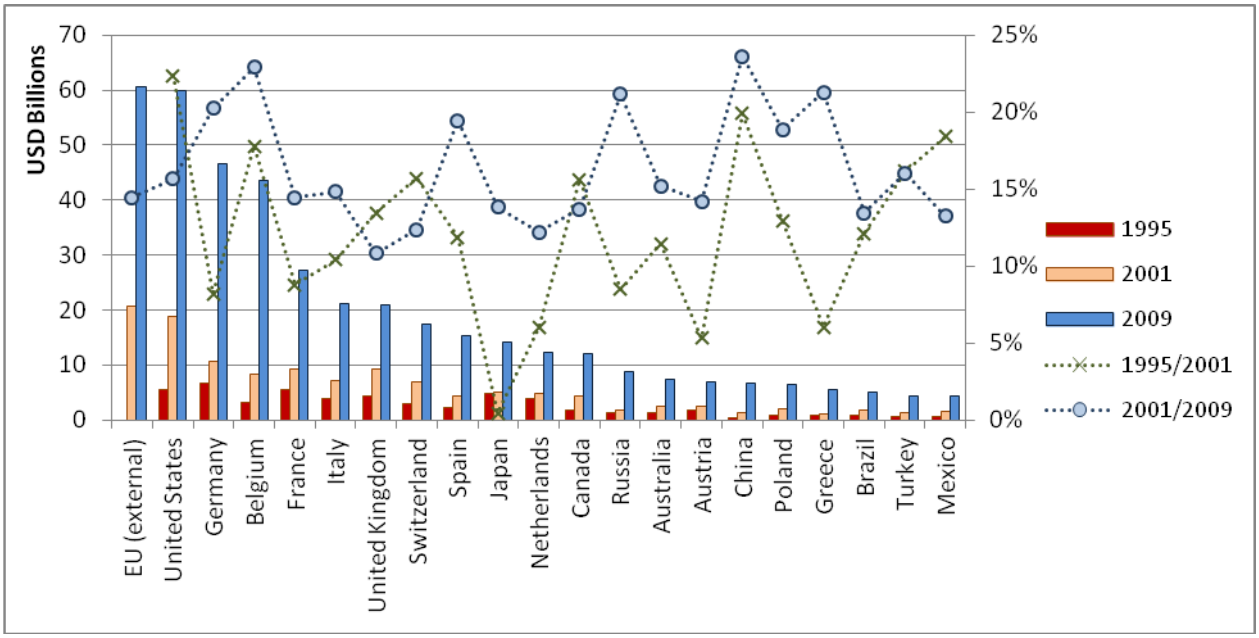


Note: Due to missing values in the database, the figure for Spain in 2009 is replaced by the figure in 2008. The figure for Belgium in 1995 is the figure for Belgium-Luxembourg.

Source: UN Comtrade

Figure 4. Major importers

Import values in 1995, 2001 and 2009, and growth rates



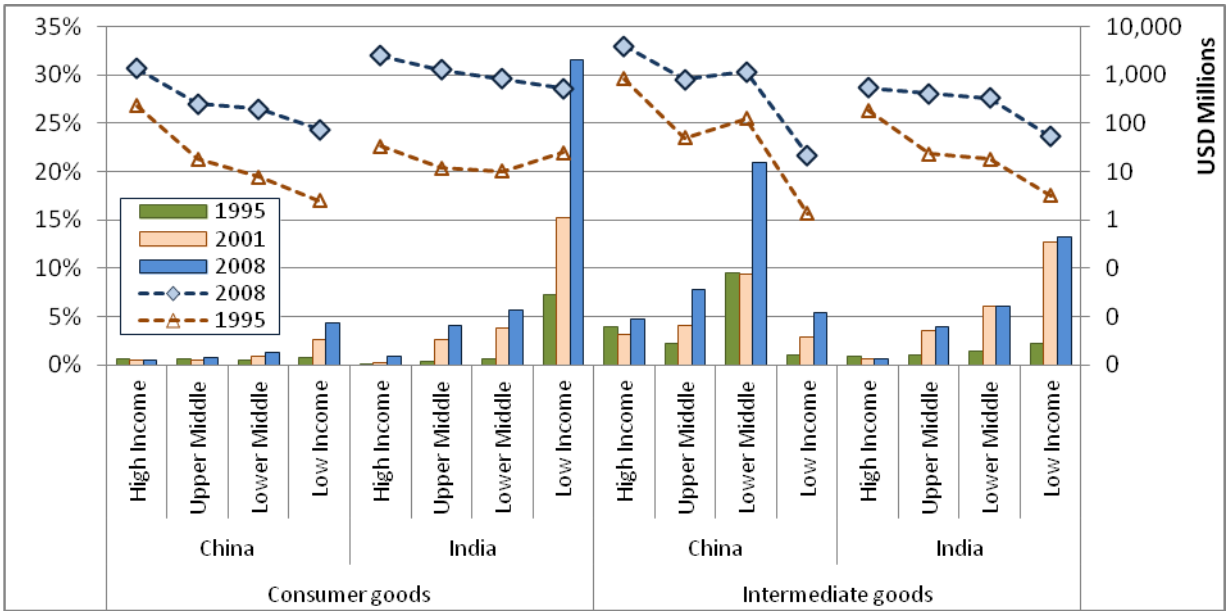
Note: Due to missing values in the database, some figures are replaced by figures in the closest years (2008 [Spain and Poland] for 2009, and 1996 [Russia] for 1995), and the growth rates in these cases are adjusted accordingly. The figure for Belgium in 1995 is the figure for Belgium-Luxembourg.

Source: UN Comtrade

Figure 5. Imports from China and India by income group

- Bar chart: share of imports from China and India in total imports

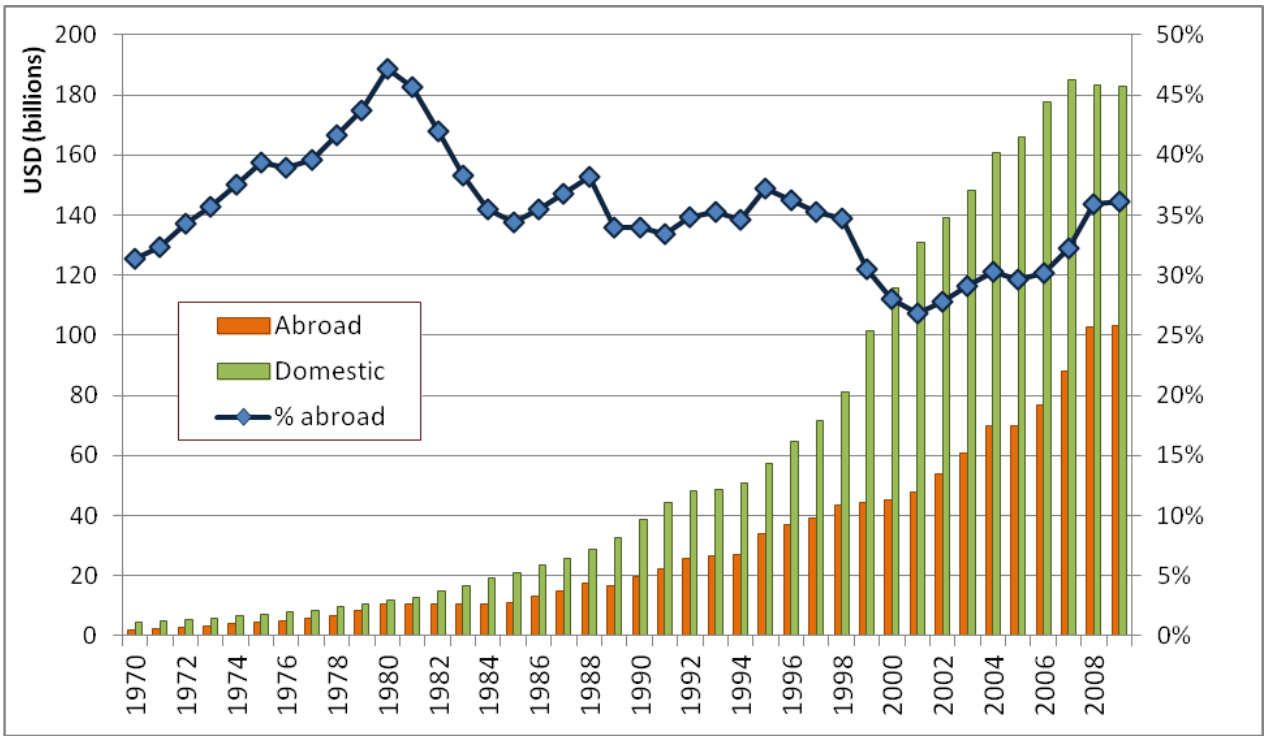
- Line chart: corresponding import values (right-hand axis)



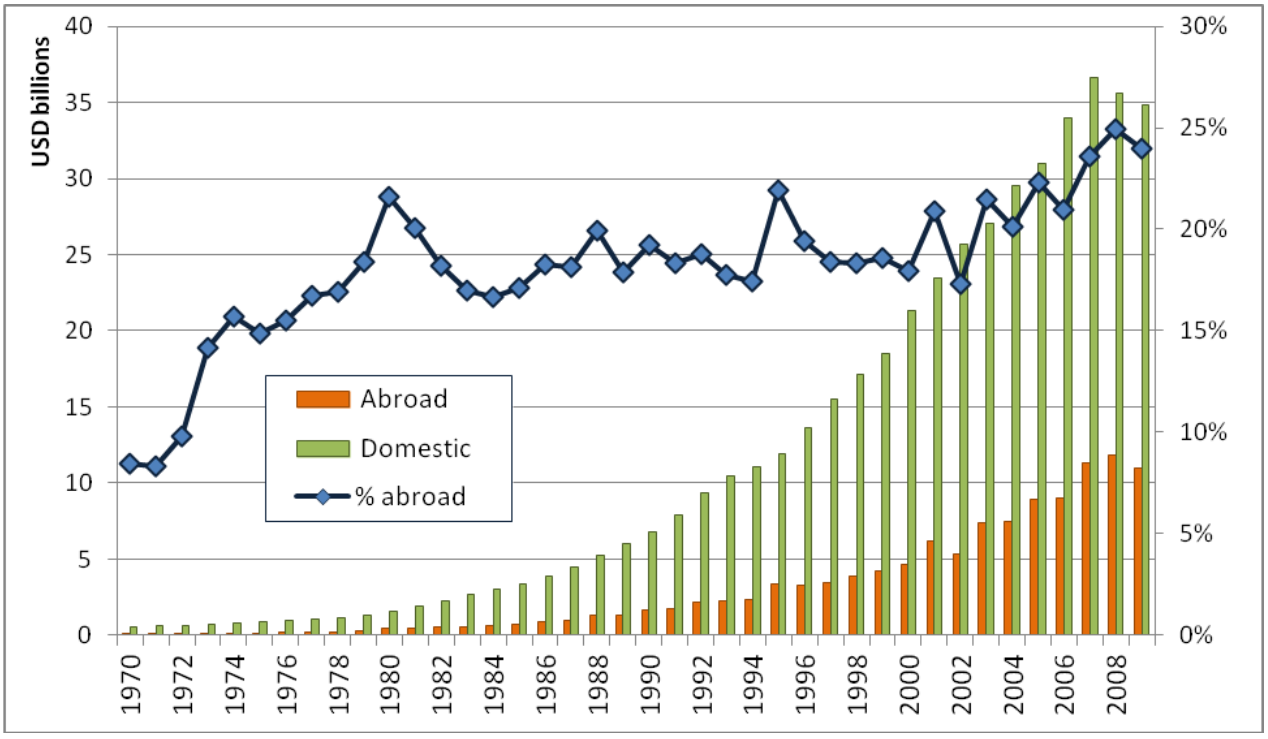
Source: UN Comtrade

Figure 6. PhRMA Member Companies

(a) Domestic sales and sales abroad



(b) Domestic R&D and R&D abroad



Note: Figures are not adjusted for inflation.

Source: PhRMA (2010), Table 1.

2. Transformation and globalisation of the R&D process

2.1 Transformation in the R&D process

2.1.1 Entry of biotech firms

R&D activities have typically been dominated by large integrated pharmaceutical companies and, in contrast to global sales activities, conventionally been carried out in-house within relatively limited geographical areas (Cockburn, 2008, 2004). In the United States, pharmaceutical companies also develop close links with academic research institutions by providing financial support for academic researchers, and their staff sometimes perform joint research with academic researchers. They also enter into co-operative research and development agreements with government laboratories, and many companies have opened new laboratories in the vicinity of top academic research institutions in order to facilitate co-operation (Sherer, 2007).

The conventional business model has been undergoing transformation since the 1980s into a more complex and fragmented structure with the entry of new biotechnology firms (Cockburn, 2004). They assumed an intermediate role between academic research institutions and established pharmaceutical companies, who transform the basic scientific knowledge discovered by universities and research institutions into viable products, and then new products are generally commercialised with established pharmaceutical companies (Rothaermel and Deeds, 2006).

Making use of additional external know-how is considered particularly important in discovery research and clinical trials for large pharmaceutical companies (Festel *et al.* 2010), and biotechnology firms collaborate with larger pharmaceutical firms at later stages such as co-manufacturing or co-marketing. Smaller biotechnology firms also collaborate with other biotechnology firms to fill the product pipeline of the latter (Chiaroni, 2008). Today, 5 out of the 10 top selling medicines in 2009 have their origin in biotech firms (PwC, 2010b).

2.1.2 Forms of collaboration

Collaborative arrangements in R&D can take various forms, such as outsourcing, alliances and in/out-licensing, and ultimately integration (Gassmann *et al.* 2008; PwC, 2010b). Industrial technology alliances are being formed each year in biotechnology in ever larger numbers, and they dominate other technology areas (Table 7; Gassmann *et al.* 2008). The patent applications with multiple applicants have seen a substantial increase since 1980, which is now much higher for pharmaceuticals-biotechnology than any other areas of technology (OECD, 2008c).[84] Survey results show that "stronger focus on partnerships/collaborations" is seen as the key changes in R&D organisation in the coming five years by 51% of the respondents in this sector (Danner *et al*. 2009).

Licensing of technologies from biotech firms to pharmaceutical companies is increasingly prevalent.[85] Over 80% of the pharmaceutical companies surveyed report

84. In particular, significant increase in co-application between business and non-business institutions is observed in pharmaceuticals-biotechnology.

85. In-licensing represents a process of sourcing and integrating the external knowledge ("the outside-in"), while out-licensing represents a process to bring ideas to market ("the inside-out). Since licensing is typically based on private contracts that are subject

increases in inward licensing in recent years (Sheehan *et al.* 2004).[86] It is expected that the in-licensed drug pipeline in the industry will double to 35% in 2002-12 (Ernst & Young, 2010a). The survey results cited above also show that "business development and in-licensing" will become more important to maximise the output of R&D operations for 52% of the respondents (Danner *et al.* 2009). Deloitte (2009, Figure 2) shows an increasing number of biotech out-licensing deals and an increasing median value of such deals between pharmaceutical and biotech companies throughout the 2000s. It further shows a shift toward compounds in the later stages of development. While 71% of biotech out-licensing in 2000 involved compounds in the early stage of development, the share has declined to 41% in 2009 (*ibid.* Figure 3). This suggests that, whereas pharmaceutical companies facing the "patent cliff" need to generate near term revenue, biotech companies need to sell off their development projects as a means of financing.

Vertical disintegration has been accompanied by horizontal consolidation over the last few decades. Waves of mergers took place in 1989 and from the mid 1990s to the mid 2000s, including those across borders (Ornaghi, 2009, Table 2C).[87] In 2009 three large scale mergers took place: Pfizer and Wyeth, Merck & Co. and Schering Plough, and Roche and Genentech). On one hand, these can be seen as a strategic response to the recent economic downturn and looming loss of patent protections, as well as gaps in the pipeline act as pressure on the industry to consolidate (Deloitte, 2009; Hornke and Mandewirth, 2010).[88]

On the other hand, more proactive motivations may be at work, such as to achieve critical mass and economies of scale and scope in activities such as R&D, including by increasing the number of therapeutic areas in their R&D programmes (Grabowski and Kyle, 2008). Moreover, the global market including emerging markets may have created a new context where mergers between big pharmaceutical companies can contribute to better performance. Larger firms may well be better at managing globalisation of clinical trials, regulatory approval processes in multiple markets, and global marketing, sales and distribution.[89]

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to confidentiality agreements, statistics on technology licensing are limited. (OECD, 2008c, pp. 21 and 70)

86. As an example, Lipitor, currently the bestselling brand, was originally in-licensed from Yamanouchi to Pfizer (Gassmann *et al.*, 2008, p. 83).

87. *See* Cleve Jones, Alistair Gray and Andrew Jack, "Dealmaking returns to pharma sector" (*www.ft.com/cms/s/0/c4e97098-17d8-11de-8c9d-0000779fd2ac.html#axzz1CJrKH36p*), including interactive graphics on pharmaceutical consolidation in 1995-2009.

88. *See also* Sarah Mishkin, "Small pharma injects growth through acquisition", *FT.com* (29 December 2010) (illustrating the recent move of smaller pharmaceutical and biotechnology firms in the UK to bolster weak drug portfolios by acquisition).

89. Carles Farkas and Tim van Bjensen, "The Real reason big pharma mergers are wise", *Forbes.com* (26 June 2009). (*www.forbes.com/2009/06/26/big-pharma-mergers-leadership-governance-acquisitions.html*)

2.1.3 Collaboration and R&D performance

Empirical evidence suggests that alliances between established pharmaceutical firms and biotechnology firms have made positive contributions to product innovation in pharmaceuticals. Rothaermel and Thursby (2007) statistically analysed the determinants of biotech patenting based on 80 pharmaceutical firms in the United States, Europe and Japan and find that R&D alliances were a statistically significant predictor of biotechnology patenting in the 1980s. They also find, however, that this relation changed in the 1990s, when R&D alliances were no longer significant in predicting biotechnology patenting, and instead R&D expenditures became a significant predictor.

Danzon *et al.* (2005) shows, based on over 1 900 compounds developed in the United States by over 900 firms in 1988-2000, that co-development across firms makes it significantly more likely to complete later phase clinical trials, but not Phase I clinical trials. In particular, the higher probability of success is detected for later stage trials when licensed from smaller firms to larger firms. It appears that small and medium size firms are capable of relatively simple and inexpensive Phase I trials, but are more likely to seek a larger partner for larger, more complex and costly Phase III trials, and in turn, large and experienced firms are competent at picking good drug candidates and/or at managing the alliances with smaller firms.

Recent empirical studies have investigated the underlying motivations for M&As and post-merger performance in this sector. They are generally consistent with the idea that companies with more pipeline problems are more likely to engage in M&As (Higgins and Rodriguez, 2006; Danzon *et al*. 2007). However, studies also tend to show that mergers may not improve business or innovative performances, especially for large firms.[90] The integration challenges associated with large M&As can be a major distraction for management (Ernst & Young, 2010c). On R&D in particular, while M&As can bring about cost reduction by eliminating duplication, and promote synergies by unifying the expertise of two companies, the large reduction in the number of researchers following a merger, together with cultural friction may hamper innovative performance (Ornaghi, 2009). However, pre-acquisition alliances can serve as a forerunner to future successful mergers (Higgins and Rodriguez, 2006). Access to information *ex ante* by the acquirer through alliances serves to reduce information asymmetry about the target companies' intangible capital, and it may also inform the parties about their potential for successful integration (Grabowski and Kyle, 2008).

90. Danzon *et al*. (2007) analysed the performance over three years after the mergers compared with the firms that did not merge, after controlling for the merger propensity. For large firms, performances of merged firms were similar to performances of firms that did not merge in many respects, the growth in operating profit was slower for merged firms, which implies greater integration efforts than anticipated. Ornaghi (2009) analysed the data for the largest pharmaceutical firms from 1988 to 2004 which cover 27 M&As and found a negative effect of mergers on R&D expenditure and patenting for three years after the merger. Munos (2009) further shows, based on 24 acquisitions and 6 mergers, there has been no increase in the expected annual NME output for larger companies.

Table 7. Industrial technology alliances in biotechnology

By country of ultimate parent company

	1980	1990	2000	2006
Worldwide	31	45	200	526
US owned	24	28	165	360
Europe owned	15	27	91	280
Japan owned	7	9	6	12
(Worldwide, all technologies)	178	385	473	898

Note: Annual counts of new technology alliances formed by domestic and multinational companies worldwide; Biotechnology includes biotechnological pharmaceuticals; alliances may be classified in more than one technology.

Source: National Science Board (2010), *Science and Engineering Indicators 2010,* appendix table 4-42.

2.2 Globalisation in R&D Process

2.2.1 Location of R&D abroad

The R&D process is not limited to activities inside national borders. In parallel with the fragmentation of the R&D process, its globalisation is on-going. In the case of US-based pharmaceutical companies, while the share of the R&D outside the United States have been stable around 25% since the late 1970s, there has been a discernible increase in the 2000s (Figure 6[b]). An increasing internationalisation of R&D has also been shown for Europe and Japanese companies (Gassmann *et al*. 2008). In particular, Swiss, Dutch and Belgian companies perform over half of their R&D outside their home country by the end of the 1980s (Gassmann and Reepmeyer, 2005).

Most of the R&D abroad by US-based companies has been performed in Western Europe, Japan and Canada (Figure 7), but their R&D activities have considerably expanded to other geographical areas especially in the emerging economies in the space of a few years (Table 8). There have been a number of investment projects in research facilities by multinational pharmaceutical companies in China and India in recent years (KPMG International, 2009c; PwC, 2010b).

Table 8. R&D by geographical area, PhRMA member companies

USD millions (share in global R&D)

	2006	2008
Brazil	25.6 (0.06%)	96.7 (0.20%)
India	8.7 (0.02%)	94.4 (0.20%)
China	32.1 (0.07%)	93.2 (0.20%)
Mexico	32.2 (0.07%)	81.2 (0.17%)
Russia	40.1* (0.08%)	80.4 (0.17%)

The figure for Russia in the 2006 column is for 2007. R&D abroad includes expenditures outside the United States by US-owned PhRMA member companies and R&D conducted abroad by the US divisions of foreign-owned PhRMA member companies. R&D performed abroad by the foreign divisions of foreign-owned PhRMA member companies is excluded.

Source: PhRMA, Profile: Pharmaceutical Industry, 2008 and 2010.

2.2.2 Outsourcing of clinical trials

While multinational outsourcing of manufacturing to low cost countries has been a common practice, outsourcing of drug development is relatively new.[91] Survey results by Ernst & Young (2010a) show that the industry is outsourcing 30-35% of manufacturing activity, and 25-35% of clinical trials. Indeed, a major redistribution of R&D activities is taking place in clinical development. Although the United States, Western Europe and Japan occupy a majority of clinical trial activity, other geographical areas such as Eastern Europe, Asia and Latin America are rapidly expanding their shares as a location of international clinical trials.[92] This is especially the case for typically large and costly later stage trials (Cockburn, 2008; Karlberg, 2009; KPMG International, 2009c, Figure 2).

Given the vast differences of the cost of clinical trials in different countries (KPMG, 2008), relocation of clinical trials is considered an important part of an effort to improve R&D performance. Garnier (2008) argues that, by switching 50% of the trials (Phase II and Phase III) from high-cost to low-cost countries (e.g. India and South America), midsize companies with 60 000 patients in clinical trials could save USD 600 million annually. A.T. Kearney (2006) suggests that, in addition to cost savings of 30-65%, in low-cost countries Phase III trials can be completed up to 6-7 months sooner than in domestic markets. David *et al.* (2009) estimates that R&D costs can be reduced by 5-10% by further outsourcing of selected non-core activities to low-cost regions.

Not only lower cost but also policy variables such as regulatory standardisation, intellectual property protection and infrastructure development, have contributed to the globalisation of clinical trials.[93] A.T. Kearney (2006) developed a "country attractiveness index for clinical trials" based on five categories of variables: patient pool (size, availability), cost efficiency (labour, facilities), regulatory conditions (e.g. regulation, intellectual property [IP] protection), relevant expertise (e.g. clinical research organisations [CROs], skilled labour force), and infrastructure and environment (e.g. IP protection, country risk). The overall results put the United States at the top, followed by China, India, Russia and Brazil.

Similarly, PwC (2008) developed a broader "outsourcing index", ranking Asian territories by cost (tax and regulatory costs, infrastructure costs, compensation and wages), risk (infrastructure, legal, economic, human capital, geopolitical) and market opportunity (current market size, market growth rate, current and future needs of healthcare). China tops the ranking, followed by India, Korea, Chinese Taipei and Japan (Figure 8).

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91. PwC (2007b, pp. 23-24) shows "low cost manufacturing" is the most frequently cited "main reason:" for outsourcing (39%) among multinationals that have outsourced, while "low cost research capacity" comes second (24%). When asked about what services they were considering outsourcing, the most frequently cited items shift to clinical trials (68%, "to a great extent" or "to some extent") and analytical services (54%) comes ahead of "large scale manufacturing of small chemical molecules" (45%).

92. Most of the major Asian clinical trial sites are hosting trials that involve multiple countries, except Japan where most of the sites are hosting trials within the country. *See* Karlberg (2008).

93. *See e.g.* Rehnquist (2001) pp. 8-9 (attributing the budding practice of clinical trials in regions that lack a history of hosting research ("emerging sites") to quick access to large numbers of trial subjects and motivation to develop a market for the study drug as well as regulatory standardisation through the ICH.)

2.2.4 Patent application and international collaboration

A sign of globalisation can also be detected in patent data, which corresponds to the earlier stage of pharmaceutical R&D. Although OECD member countries account for over 90% of world patent applications in biotechnology and pharmaceuticals, emerging economies have expanded their shares in the 2000s (Table 9), and China and India are now among the top 10 (Figure 9).

Table 9. Patent applications by the inventor's country of residence

Under the Patent Cooperation Treaty (PCT) at international phase, European Patent Office (EPO) designations

	Biotechnology (15)		Pharmaceuticals (16)	
	2001	**2007**	**2001**	**2007**
China	50 (0.9%)	88 (1.6%)	150 (1.4%)	400 (3.4%)
India	28 (0.5%)	45 (0.8%)	124 (1.1%)	320 (2.7%)
Russia	35 (0.6%)	39 (0.7%)	35 (0.3%)	108 (0.9%)
Brazil	8 (0.1%)	25 (0.5%)	28 (0.3%)	43 (0.4%)
OECD	5 329 (97.0%)	5 052 (94.3%)	10 323 (95.3%)	10 587 (90.8%)
World	5 493 (100%)	5 358 (100%)	10 828 (100%)	11 655 (100%)

Note: Technology classifications are in reference to "new concept of technology classification" in Schmoch (2008), p.9.

Source: OECD Patent Database

The patterns of co-invention (patent application with foreign co-inventor[s]) are indicative of the state of international collaboration in drug discovery. The overall shares of co-invention have been stable for both pharmaceuticals and biotechnology during the former half of the 2000s (around 13% and 11%). The shares are over 20% in many countries (2005-07 average), with notable exceptions of Japan (7%, 8%) and Korea (7%, 12%). In contrast, over 50% of patent applications are co-inventions in Switzerland and Belgium (Figure 9).

International licensing is another indicator of globalisation of the R&D process. Although systematic data are not available, a study in the United States shows that international in-licensing is particularly wide-spread in the pharmaceuticals sector (Robbins, 2006). While overall US industry receives royalties and license fees from unaffiliated foreigners much more than it pays to them, the US pharmaceutical firms make substantially higher payments to foreign parties on royalties and license fees for industrial process[94] than they receive (in 2002). The majority of payments for industrial process by US industry are reported by the pharmaceutical industry.

2.3 Globalisation of R&D process and organisational innovation

The fragmentation and globalisation of the R&D process are supposed to bring about substantial efficiency gains. Large pharmaceutical companies need leading edge external know-how and low cost services, and small biotech companies need a wider range of expertise outside of their core competences (Festel *et al.* 2010; Danzon *et al.* 2005).

94. This includes the use, sale or purchase of intangibles that are used in connection to the production of goods as well as technology licensing fees, royalties, and payments for the use of patents, trade secrets, and other proprietary rights used in the production of goods. (Robbins, 2006, p. 36)

Specialisation and competition in a global market for technology can make drug development faster and more cost effective than decision making by internal bureaucracies (Cockburn, 2008, 2004; Garnier, 2008). Innovation with the external world, involving different parties, is widely believed to be the model of R&D in the future (Ernst & Young, 2010b; Danner *et al*. 2009).

On the other hand, this can also be another source of inefficiency. Information asymmetry about the value of technologies and difficulties in writing up workable contracts[95] can distort the market for technology, resulting in inefficient allocation of resources, and wasteful bargaining and other transaction costs will reduce value creation (Cockburn, 2004, 2006). This is more likely to be the case with upstream drug discovery because of higher complexity and uncertainties involved (Gassmann and Reepmeyer, 2004; Rothaermel and Deeds, 2006).[96] Moreover, management of cross-border R&D activities involves a significantly higher degree of complexity (Gassmann and Reepmeyer, 2004; Gassmann *et al.* 2008).

For these reasons, balancing the cost and benefit of outsourcing and off-shoring of R&D activities has become an important issue of R&D management, and pharmaceutical companies have moved to redesign their R&D departments to cope with these new challenges. For example, Novartis established Novartis Institutes for BioMedical Research (NIBR) in 2002 in the vicinity of Harvard and the MIT, away from its headquarters, which manages the network of research institutes located in the United States, Switzerland, United Kingdom and China (Gassmann and Reepmeyer, 2004; company website). GalaxoSmithKline decided to break the pyramid structure of R&D into a constellation of highly focused centres with CEOs who have the authority to initiate or terminate a project and make outsourcing decisions. It has further taken an initiative to break the staff into smaller groups since 2008[97] (Garnier, 2008; Grabowski and Kyle, 2008).[98]

Eli Lilly is transforming itself into a "fully integrated pharmaceutical network", in place of "fully integrated pharmaceutical company" (Ernst & Young, 2010c). For example, it sold its laboratory facilities and operation located in India to a clinical research organisation (CRO) with which it established a long-term relationship. Similarly, it chose to partner with a Chinese firm for chemistry services, instead of building its own facility in China. For discovery and development of molecules, it has signed risk-and-reward sharing deals with Chinese and Indian firms. It also established venture

95. One typical issue associated with information asymmetry is "lemons" problem. Small biotech firms may develop superior compounds and out-license less promising ones, taking advantage of their superior information. The empirical evidence is mixed, but recent study by Arora *et al*. (2007), based on 3 311 R&D projects in the world in 1980-94, finds no evidence to support this "lemons" theory.

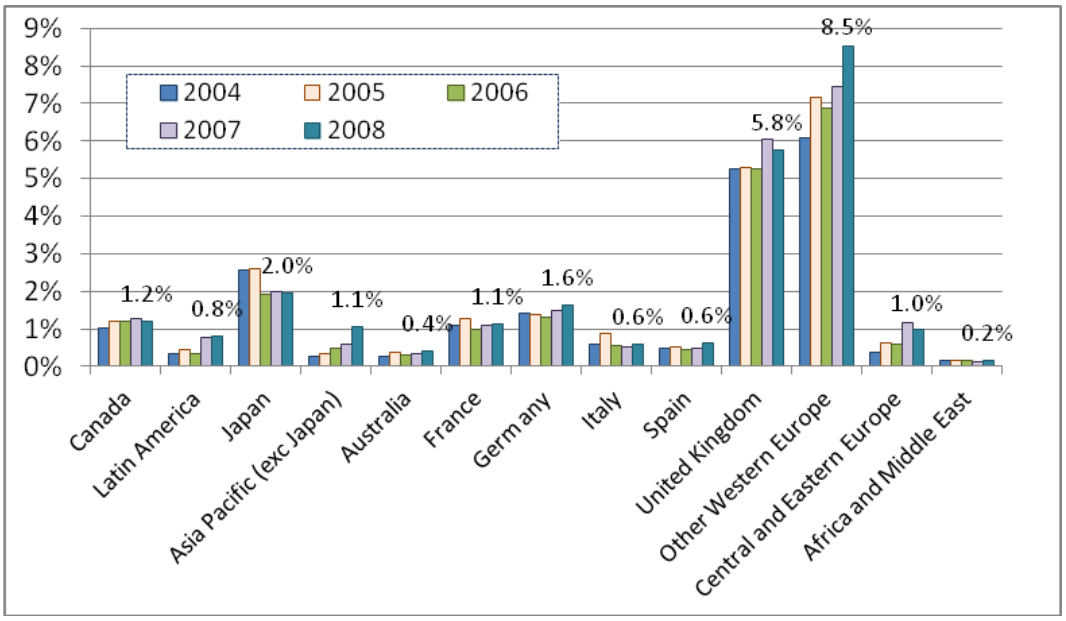
96. Reflecting the different nature of outsourcing areas, co-operation models employed are also different: while service providers are typically selected on a project-by-project basis from a short list of preselected providers for many types of services (e.g. clinical trials), strategic partnership where a framework contract covers all the relevant services is predominant for discovery research and chemical synthesis. (Festel *et al*., 2010, pp. 92-93)

97. Jeanne Whalen, "Glaxo Tries Biotech Model to Spur Drug Innovations", *WSJ.com* (1 July 2010).

98. More examples are reported in Gassmann *et al.* (2008) Chapter VI.

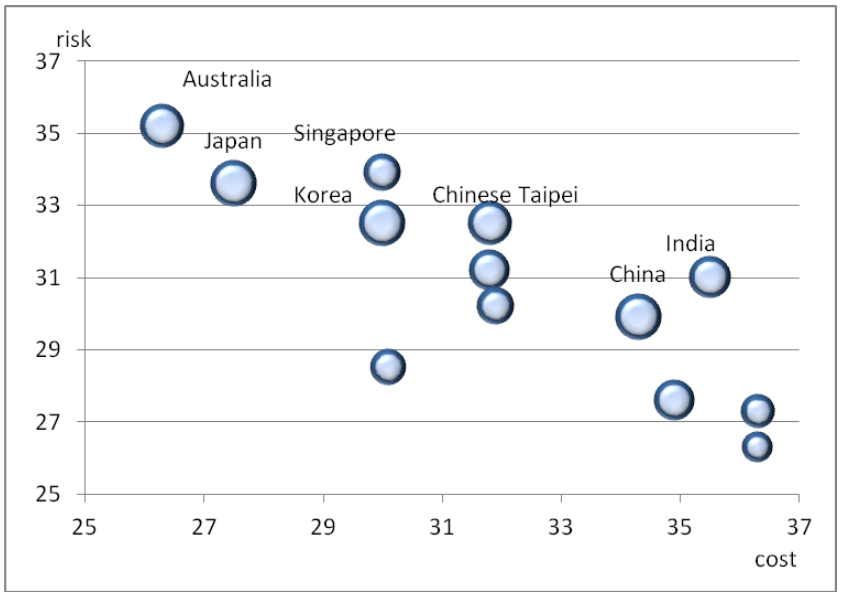
funds to support equity investment and partnership around the world. Together these are intended to leverage its own capacity and to attract resources from its partners.

Figure 7. R&D share by geographical area, PhRMA member companies



Source: PhRMA (2010), Table 6 and corresponding tables in previous issues.

Figure 8. Outsourcing index, plotted by cost and risk factors

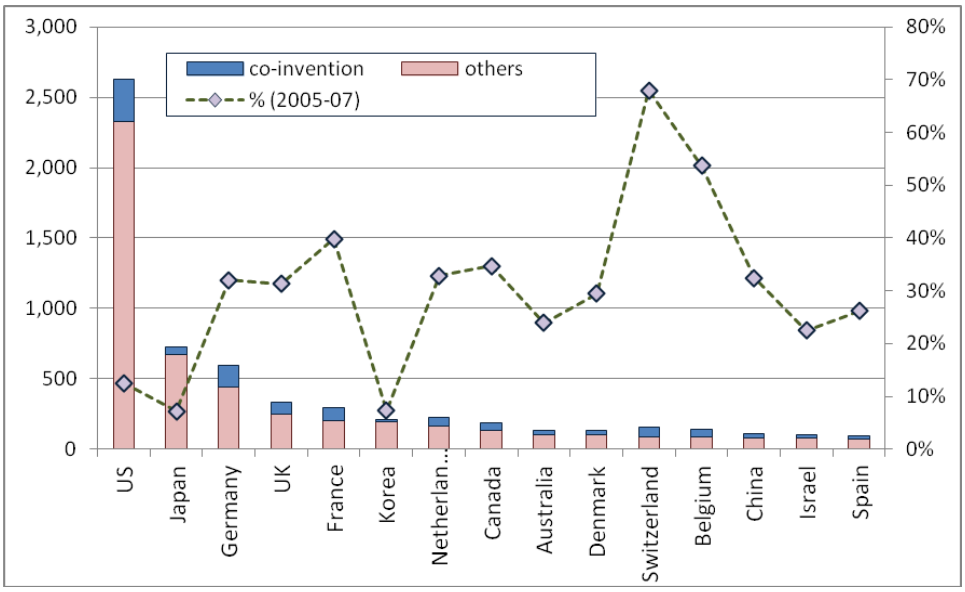


Note: The horizontal axis represents cost score, vertical axis represents risk score and the size of the bubble represents market opportunity score.

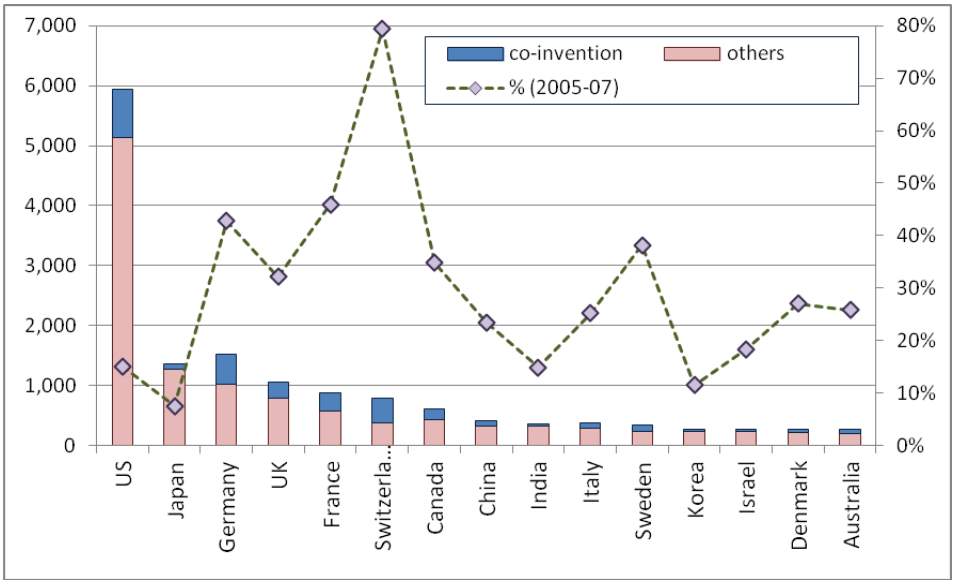
Source: PwC (2008b)

Figure 9. Patents with foreign co-inventors (patent applications filed under the PCT, at international phase, EPO designations), 2005-07 average

(a) biotechnology



(b) pharmaceuticals



Source: OECD Patent Database.

2.4 Growing R&D capability of the emerging economies

The pharmaceutical companies in emerging economies are increasing their own R&D capabilities. For example, leading companies in India are moving to more R&D oriented businesses.[99] Introduction of product patent in 2005, in compliance with TRIPS agreement, as well as import liberalisation measures under the Pharmaceuticals Policy in 2002,[100] has given these companies incentive to be more innovative. The rules on clinical trials have been made more consistent with international practice,[101] such regulatory initiatives have contributed to establishing India's reputation as a reliable destination for clinical trials (KPMG International, 2009).

Arora *et al*. (2008) shows a sharp increase in R&D intensity (R&D/Sales ratio) in 2005 (from 4.2% in 2004 to 8.5% in 2005) and a sharp increase in innovative output (patent counts) in the 2000s in India. R&D intensity exceeded 10% in a few research-based companies in 2005-06, up from 3-4% in 1999-2000 (Prahalathan and Baruah, 2007). Some companies have started their own original research into new chemical entities and novel drug delivery systems (PwC, 2010a). For the economy as a whole, pharmaceutical industry is a key player in the Indian innovation system, accounting for 20% of total R&D expenditures (OECD, 2010a).

Various aspects of foreign contact play a vital role in upgrading R&D capability. The participation in foreign-commissioned clinical trials has been contributing to raising their standard. Although India lacked the expertise on clinical trials when product innovation was absent from the industry, many contract research organisations (CROs) and multinational companies started clinical trials in India, and Indian firms dealing with foreign clients or exporting to foreign regulated markets are looking to obtain necessary certifications (Good Laboratory Practice [GLP], Good Clinical Practice [GCP]) (PwC, 2010a; Rituparna Maiti and Raghavendra M. 2007). In the case of drug candidates originally formulated by Indian firms, partnership with multinational is essential to push a drug they initially formulated through the pipeline in order to bear the high costs and risk of failure. Several Indian firms have already entered into research partnership with multinationals. (PwC, 2010b; KMPG, 2008) Some leading companies have become highly outward oriented. Approximately 80% of the total sales by Ranbaxy are generated

99. *See* Balcet and Bruschieri (2008, pp. 15-45) for a case study on two of the leading pharmaceutical companies in India, Nicholas Piramal nad Sun Pharmaceutical Industries.

100. The scope of industrial licensing was reduced and tariff and non-tariff barriers were brought down under the liberalization policies (Prahalathan and Baruah, 2007, p. 69).

101. The amendment to Schedule Y of the Drug and Cosmetics Act in 2005 lays out the rules on clinical trials. This incorporated Good Manufacturing Practice (GCP) guideline of 2001, which was "evolved with consideration of WHO, ICH, USFDA and European GCP guidelines […]", and "[t]hey should be followed for carrying out all biomedical research in India at all stages of drug development." India's Good Laboratory Practice (GLP) is in line with the OECD principles (Manni, 2006, p. 22), and the National GLP Compliance Monitoring Authority was established in 2002, although certification of GLP remains a voluntary process (PwC, 2010c, pp. 16-17). However, the actual number of certified sites and laboratories may not be adequate to meet the demand (PwC, 2010, p. 16; Maiti and Raghavendra M., 2007, p. 9; Vijay, 2010). It continues to be a challenge, although improving, to ensure the compliance with all relevant regulation when outsourcing a research to India (PwC, 2010c, p. 24).

abroad, including the US (nearly 30% of its total sales) and Europe (nearly 20%) (Perlitz, 2008). Nicolas Piramal generated over 44% of consolidated revenues from outside India, and foreign/total sales ratio reached 54.8% for Sun Pharmaceutical, both in 2008 (Balcet and Bruschieri, 2008).

Moreover, leading Indian pharmaceutical companies have been active in overseas acquisition in order to overcome their internal innovation capacity limits by acquiring new products, new markets, skills and technologies (Pradhan, 2008). Conversely, divestiture of existing businesses can provide essential financial resources for product innovation. This is the case with the Piramal group, which sold its generic drugs unit to Abbott Laboratories (United States) and now plans to use the proceeds to launch its own drug (and the first domestically developed drug in India) by 2012.[102]

China has emerged as a highly favoured location of outsourcing (2.2.2 *supra*). Many global players have set up R&D facilities in recent years, and the process of globalisation of R&D with multinational companies is increasingly a key driving force for the R&D investment in China (Hamdouch and He, 2009). The CROs in China is growing, and they have developed drug discovery services by attracting skilled professionals from the United States, Japan and other countries.[103] Large- and medium-sized pharmaceutical companies are also outsourcing discovery research to companies in China as well as in India.

Biomedicine was identified as one of the strategic focus areas under the 11th Five-Year Plan (2006-10) by the Chinese Government.[104] In 2009, the Government announced a spending programme to support several industrial technologies, including biotechnology. The State Food and Drug Administration (SFDA) issued its special procedure to accelerate the approval of certain types of drugs. China's accession to the WTO and thus TRIPS agreement is perceived as a significant improvement in business environment (KPMG International, 2009c). The legislation to further strengthen intellectual property came into effect in October 2009. Life Science Parks have been set up at various locations, especially in Shanghai and Beijing to facilitate foreign investment in pharmaceutical and biotechnology sectors.[105]

Brazil introduced product patent in 1996, much earlier than the deadline set by TRIPS agreement, as a part of their economic reform initiatives. Laforgia *et al*. (2007) shows that this patent reform had a substantially positive impact on the overall number of patent applications in Brazil, although they also find that the great majority of these new patent applications have come from non-residents. Specifically on the pharmaceuticals sector, the upsurge came after 2001, and five large multinationals account for more than one fifth of pharmaceutical patent in 2001-04. A case study on the domestic firms and research

102. James Fontanell-Kahn and Joe Leahy, "Piramal to launch own drug 'by 2010'", *FT.com* (27 May 2010). Recent high-profile foreign takeover deals is reportedly prompting the government to consider imposing limits on foreign ownership of domestic pharmaceutical companies, which currently does not exist. Girija Shivakumar nad Amy Kazmin, "India eyes drug industry ownership curbs", *FT.com* (3 January 2011).

103. "China's Pharma Leaps into Discovery", *Chemical & Engineering News*, Volume 86, Number 05 (4 February 2008).

104. This paragraph draws on Ernst & Young (2010c) pp. 30-33.

105. *See* Hamdouch and He (2009, p. 110-111) for an example of Shanghai Zhangjiang Life Science Park

institutions in the State of Sao Paulo shows the role of patent to encourage entrepreneurs to invest in bio-medical innovation and facilitate building network with local research institutes (Ryan, 2010). In recent years, the government is encouraging technology transfer from multinationals as a part of a deal to award a contract to supply certain pharmaceutical products to the domestic market.[106]

3. Trade policy issues

3.1 Tariff elimination in the Uruguay Round

Against the backdrop of globalisation of the pharmaceutical sector, there have been major multilateral initiatives that have affected pharmaceuticals trade since the 1990s, many of which arose as a result of the Uruguay Round (1986-94). Among them was tariff elimination in the pharmaceutical sector agreed among most of the OECD countries.[107] The participants in this initiative agreed to bind their tariffs on pharmaceuticals at zero, and to eliminate their applied tariffs on the date of entry into force of the WTO agreement. There have subsequently been four rounds of reviews of the product coverage resulting in tariff elimination for additional products. The review process is largely industry driven, with the input from the International Committee to Eliminate Pharmaceutical Tariffs (INTERCEPT), in which European, Japanese and US industries participate (European Parliament, 2010). Further tariff elimination for pharmaceuticals alongside other healthcare products has been proposed in the current DDA negotiations.[108]

The tariff rates have been coming down since the conclusion of the Uruguay Round. Pharmaceutical imports by the participants to the pharmaceuticals initiative in the Uruguay Round are essentially duty free. Other countries have also reduced their tariffs on pharmaceuticals, either due to WTO commitments at their accession or those in the Uruguay Round, or as unilateral initiatives. Still, average MFN applied tariff rates of major non-participating countries remain non-negligible. As a result of all these, it is estimated that nearly 60% of the world's tariff revenue is collected by 10 major non-OECD members who did not participate in the pharmaceutical tariff elimination. New WTO members and other OECD members each collects about 11% (Table 10).

Figure 10 shows the estimated average effective tariff rates by these groups imposed on imports as categorised by income levels of the originating countries.[109] This shows

106. Andrew Jack, "Brazil's prescription for pharma", *FT.com* (22 December 2010).

107. GATT (1994), *Trade in Pharmaceutical Products*, L/7430 (25 March 1994).

108. "Draft Modalities for Open Access to Enhanced Healthcare", submitted by Singapore, Switzerland, Chinese Taipei and the United States, in Fourth Revision of Draft Modalities for Non-Agricultural Market Access (TN/MA/W/103/Rev.3, 6 December 2008). *See generally* TAD/TC/WP(2010)9/FINAL, Box 1.

109. Effective average tariff rates by income groups are calculated as [estimated tariff revenue collected from imports, aggregated by income group of originating countries]/[import value from the same group of originating countries]. Figures from 2007 are used where 2008 figures are not available; neither was available for some countries at the time of compilation of the data (e.g. Thailand). "Others" contains all countries not being a part of any of the groups referred to in the graph, as long as contained in the database. Income group classification is in accordance with the World Bank (September 2010).

that, whereas tariff barriers by participants in the Uruguay Round initiative are minimal, the tariffs imposed by many countries in the "other non-participants" group remain high, including on the imports from lower income countries. The average tariff barriers imposed by recently acceded WTO members are no more than 2%.

Finally, it must be noted that pharmaceutical sector often enjoys exemptions, waivers and reductions of tariffs, although systematic information is not available, therefore the actual amount of tariff revenues from pharmaceuticals may well be below the estimate shown here (Olcay and Laing, 2005). Even if tariff rates are low, Cameron *et al*. (2009) shows that taxes and duties can have a large cumulative effect when applied early in the supply chain, adding costs for the consumers.

Table 10. Average applied MFN tariffs and estimate of tariff revenue share by group

	Simple average		Weighted average		Tariff revenue (% share)	
	2001	2008	2001	2008	2001	2008
UR Pharma participants	0.93%	0.15%	0.07%	0.01%	2.4%	0.4%
Other OECD members	4.62%	3.80%	5.38%	4.75%	16.7%	8.7%
New WTO members	4.00%	1.03%	7.32%	2.04%	15.0%	12.2%
Other non-participants	9.14%	5.81%	9.53%	7.58%	50.1%	66.8%

Notes:

1. "UR Pharma participants" refers to the participants in the tariff elimination initiative in pharmaceuticals in the Uruguay Round and subsequently acceded member states to the EU that is: Australia, Canada, the European Union (27), Iceland, Japan, New Zealand, Norway, Singapore, Switzerland, the United States (Hoda (2001), p.29); "Other OECD members" refers to the OECD members except above listed countries (Chile, Israel, Korea, Mexico, Turkey); "New WTO members" refers to recently acceded members to the WTO after its establishment in 1995 (Albania, Armenia, China, Chinese Taipei, Croatia, Ecuador, Georgia, Jordan, Kyrgyz Republic, FYR Macedonia, Moldova, Mongolia, Oman, Panama, Saudi Arabia, Tonga, Ukraine Vietnam) except least developed countries (LDCs) as defined by the United Nations at the time of accession (Cambodia, Cape Verde and Nepal) and EU member states; "Other non-participants" refers to top 10 traders (exports + imports) in 2008 excluding those in the previous categories (Algeria, Argentina, Brazil, Colombia, Egypt, India, Russia, South Africa, Thailand, Venezuela). However, due to missing data in the databases Tonga and Ukraine are not included in the calculation, nor are Saudi Arabia (2001), Thailand (2008) and Vietnam (2008).

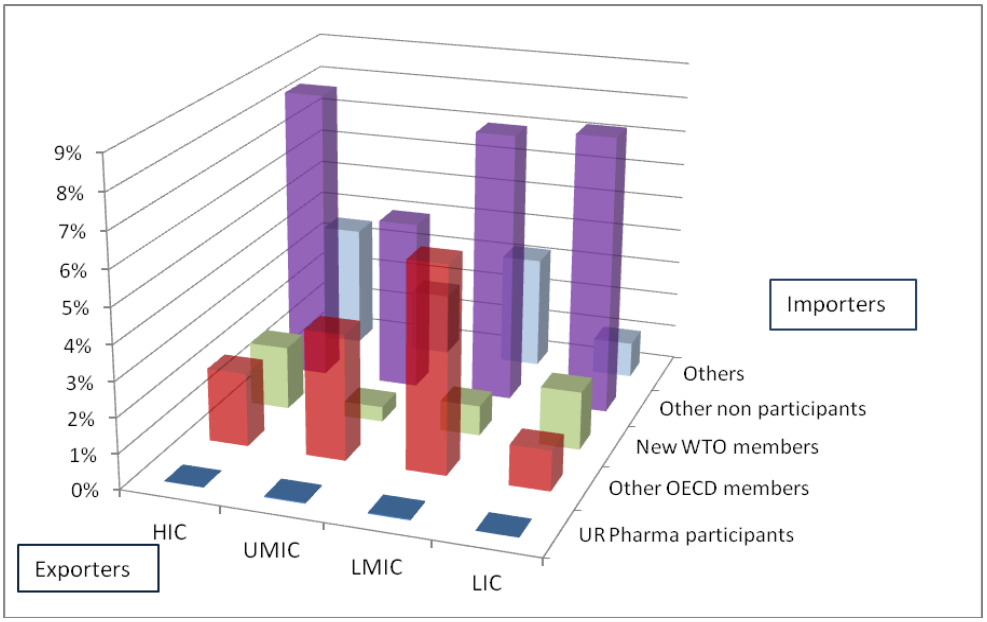
2. "Simple average" is calculated by taking the simple average of each country's simple average MFN applied tariffs for the pharmaceuticals (generated by the database) within the country group; "weighted average" is the average of weighted average MFN applied tariffs for the pharmaceuticals (generated by the database) weighed by import share within the country group. "Tariff revenue" is calculated by [weighted average of effective applied tariffs] x [import value]. "Effective applied tariffs" in this calculation reflect preferential tariffs beyond MFN applied tariffs. However, the amount of duties actually collected at customs is not identical to this calculation because of rules of origin, special incentive schemes and other factors that are not reflected in duty rates in the database.

3. Tariff revenue is expressed in terms of the share in the world, which covers all countries in the database not included in any of the groups in the table, therefore the figures do not add up to 100%.

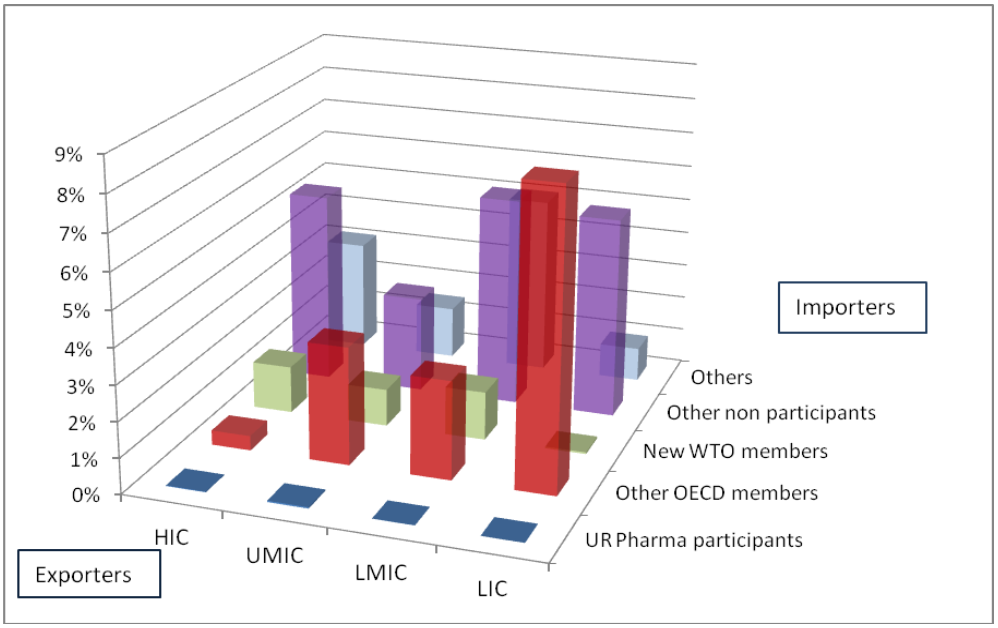
Source: UNCTAD TRAINS, supplemented by WTO IDB, extracted from WITS.

Figure 10. Average effective tariff rates by country group pair

(a) consumer goods (2008)



(b) intermediate goods (2008)



Note*:* UMIC: upper-middle-income countries: LMIC: lower-middle-income countries; LIC: low-income countries

Source: UNCTD, TRAINS; WTO, IDB

3.2 Regulatory measures

Pharmaceutical products are extensively regulated in order to ensure their safety and efficacy. Given their possible effects on trade, considerable progress has been made in various forms to enhance transparency and reduce complexity involving such regulations.

3.2.1 TBT Agreement

Under the rules of the WTO, in particular the Agreement on Technical Barriers to Trade (TBT Agreement), WTO members need to ensure that that technical regulations and standards do not create unnecessary obstacles to international trade, while recognising the policy objectives of "the protection of human, animal or plant life or health, of the environment, or for the prevention of deceptive practices" (TBT Agreement, preamble).

Under the terms of the Agreement, WTO members notify a technical regulation when a relevant international standard does not exist and if the technical regulation may have a significant effect on trade (TBT Agreement, Article 2.9; Article 5.6 for conformity assessment procedure). In addition, "specific trade concerns" can be raised and discussed at meetings of WTO's Committee on Technical Barriers to Trade (TBT Committee), including measures not notified through this procedure. In 2009-10, three issues involving pharmaceuticals were raised at the Committee meetings (Table 11).

The TBT Agreement is a horizontal instrument rather than covering specific sectors. Whereas several sector specific negotiating proposals to address technical barriers have been tabled in the current DDA negotiations, no proposal has been made on pharmaceuticals.

Table 11. Specific trade concerns raised in 2009-10 at the TBT Committee meetings involving pharmaceuticals

Title	Member(s) concerned	First raised	Concerns raised
Argentina – Measures affecting market access for pharmaceutical products	Chile, Colombia, Paraguay	09-11-2007	A system for the entry of pharmaceuticals into the market: the classification of countries and the resulting application of conformity assessment procedures; the classification and application of tariffs or fees for verification visits to plants located in the countries of origin.
Indonesia – Regulation of BPOM No. HK.00.05.1.23.3516 relating to distribution license requirements for certain drug products, cosmetics, food supplements, and food	EU, US	05-11-2009	A new requirement for producers of food, food supplements, drugs and cosmetics to obtain distribution licenses.
Turkey – New conformity assessment procedures for pharmaceuticals	EU Switzerland, US	24-03-2010	Foreign producers were required to have their manufacturing plants inspected by the authority which would issue a good manufacturing practice (GMP) certificate; stopped accepting the GMP certificates by foreign regulatory authorities.

Source: The WTO, *TBT Information Management System*; the minutes of the TBT Committee meetings.

3.2.2 ICH: Regulatory harmonisation[110]

Outside of the WTO, sector specific initiatives among the regulators and the industry in major pharmaceuticals producing regions have been taken under the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use). The ICH was established in 1990 "[t]o maintain a forum for a constructive dialogue between regulatory authorities and the pharmaceutical industry on the real and perceived differences in the technical requirements for product registration in the EU, USA and Japan in order to ensure a more timely introduction of new medicinal products, and their availability to patients" (Revised ICH terms of reference). The ICH is comprised of six parties which represent the regulatory bodies and the research-based industry in the EU, Japan and the United States. The World Health Organization (WHO), the European Free Trade Association (EFTA) and Canada hold observer status.

Over 50 guidelines have been completed in four categories (quality, safety, efficacy and multidisciplinary) and implemented in the three participating regions. Among the major achievements has been the Common Technical Document (CTD) (agreed in 2000), which provides for a harmonised structure and format for new product applications, avoiding the need to generate and compile different registration dossiers. Specifications for new drug substances and products were agreed (1999) to improve the situation where conflicting standards were set for the same product in different regions, leading to increased expenses and risks of error as well as a potential cause for interruption of product supply. Another achievement to note is the Guideline for Good Clinical Practice (GCP) (1996), an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. This provides a unified standard for the three regions to facilitate the mutual acceptance of clinical data by the regulatory authorities.

The ICH has been seeking to establish partnership with regional groupings such as the Asia-Pacific Economic Cooperation (APEC), the Association of Southeast Asian Nations (ASEAN), the Gulf Cooperation Council (GCC), the Pan American Network on Drug Regulatory Harmonization (PANDRH) and the Southern African Development Community (SADC). It has further extended such efforts to include individual drug regulatory authorities such as those in Australia, Brazil, China, Chinese Taipei, India, Russia, Singapore and Korea, with a view to reducing differences in technical requirements that impact on the availability and cost of new medicines, to promote international movement of pharmaceuticals that are safe, effective and of high quality, and to promote the conduct of clinical trials and data collection that meet international standards.

The driving force of this harmonisation effort has been the globalisation of the pharmaceuticals market, the need to curb R&D spending and healthcare costs, and to facilitate faster and safer access to new medicines. Karlberg (2008) argues that the globalisation of clinical trials is a consequence of the ICH GCP, "since pharmaceutical companies can now collect trial data worldwide, rather than only in established regions, for filing new drug applications also in established regions." The harmonisation efforts may have further contributed to changing the regulatory culture, i.e. as Rehnquist (2001) notes, regulatory authorities have become increasingly willing to accept data from foreign

110. The description draws on Branch (2005) and the ICH website; *see cf.* Tarabusi and Vickery (1995) p. 102; Matraves (1999) p. 176.

research as part of a new drug application. ICH GCP "is *de facto* recognised worldwide as *the* applicable standard for GCP" (European Commission, 2009b [italics in the original]),[111] and the fact that ICH guidelines are being used as a useful vehicle for harmonisation initiatives at a regional level among non-ICH members (WHO, 2002; 2.4 *supra* [GCP in India]) can also be viewed as one indication of their usefulness.

3.2.3 PIC/S: harmonisation of GMP standards

The Pharmaceutical Inspection Co-operation Scheme (PIC/S) is an informal arrangement between regulatory authorities aiming at harmonising inspection procedures worldwide by developing common standards specifically in the field of good manufacturing practice (GMP). While it has its roots in Pharmaceutical Inspection Convention (PIC) among EFTA members in 1970 (PIC/S, 2005), PIC/S members now includes a number of non-European countries: Argentina, Australia, Canada, Israel, Malaysia, Singapore and South Africa, as well as the United States, the most recently acceded member on 1 January 2011.

The original PIC/S GMP Guide was derived from the WHO GMP Guide, and have seen been developed to incorporate more stringent manufacturing and health requirements in member countries and to keep pace with technological developments. The PIC/S members are expected to use PIC/S GMP guides, but, unlike the case under a mutual recognition agreement (MRA), they are not required to accept the inspection results by authorities of other countries (PIC/S, 2005). Harmonisation of GMP standards may imply reduced duplication of inspections and cost savings for both manufacturers and regulatory authorities, even without a formal MRA (PIC/S, 2005). This can ultimately facilitate trade and enhance access to pharmaceutical products. Other benefits of PIC/S membership include training opportunities, networking, information sharing GMP inspection reports and rapid alert system on defective medicinal products.

3.2.4 OECD: GLP and mutual acceptance of data (MAD)

Under the OECD Decisions[112] which make up the Mutual Acceptance of Data (MAD) system, data generated in the pre-clinical safety testing of chemicals in an OECD Member country or full adherent in accordance with OECD Test Guidelines and OECD Principles of Good Laboratory Practice shall be accepted in other Member countries and adhering countries for purposes of assessment and other uses relating to the protection of man and the environment. Singapore and South Africa are full adherents, and India, Brazil, Argentina, Malaysia and Thailand are provisional adherents. (Provisional adherence to the OECD system means that the non-member must accept data from OECD countries and full adherents generated under MAD conditions, but OECD members and adherents are not obligated to accept data from the non-member.)

111. "ICH GCP has been the 'bible' for CRAs, auditors and other clinical research professionals worldwide". Andrew Smith (2009), "Still relevant after all these years? Should ICH GCP be reviewed & revised?", Clinical Research focus (September 2009).

112. Decision of the Council concerning the Mutual Acceptance of Data in the Assessment of Chemicals [C(81)30(Final)]; Decision-Recommendation of the Council on Compliance with Principles of Good Laboratory Practice [C(89)87/FINAL]; Decision of the Council concerning the Adherence of non-Member Countries to the Council Acts related to the Mutual Acceptance of Data in the Assessment of Chemicals [C(97)114/FINAL]

For pharmaceuticals, the MAD system has meant alleviation of conflicting or duplicative requirements by different authorities. In 1998, OECD (1998) estimated that the annual cost savings involving new pharmaceuticals amount to EUR 33 million.[113] An updated estimate in 2010, which did not include pharmaceuticals, found about 150% increase of cost savings for the chemicals industry (OECD, 2010b).

3.2.5 Regional harmonisation initiatives in ASEAN

Regulatory harmonisation initiatives in pharmaceuticals are underway also at a regional level, working with international bodies such as the ICH and the WHO. Among them, the ASEAN (Association of Southeast Asian Nations) is making solid progress in regulatory harmonisation in pharmaceuticals, as a part of the efforts to achieve the ultimate goal of regional economic integration. In January 2009, two harmonisation instruments were adopted and implemented: ASEAN Common Technical Requirement (ACTR) and ASEAN Common Technical Dossier. ACTR is a set of written materials intended to guide applicants to prepare application dossiers in a way that is consistent with the expectations of all ASEAN regulatory authorities, covering quality, safety and efficacy, and a number of ICH guidelines are adopted without modification. ACTD is the part of the marketing authorisation application dossier that is common to all ASEAN member countries.[114]

In April 2009, ASEAN Economic Ministers signed the ASEAN Sectoral Mutual Recognition Arrangement (MRA) for Good Manufacturing Practice (GMP) Inspection of Manufacturers of Medicinal Products. Under this MRA, each party shall accept GMP certificates or inspection reports issed by other inspection authorities (Article 2). This means that GMP certifications and/or inspection reports will be used as a basis for regulatory actions such as the granting of approvals or licenses, and post-market assessments of conformity (Article 1). Manufacturers need to comply with the PIC/S Guide to GMP for Medicinal Products or equivalent GMP code, and are regularly inspected by the national authority (Article 8). This MRA is to be fully implemented starting January 2011 (Article 19).

This MRA is expected to help manufacturers to demonstrate that the medicinal products in the ASEAN are consistently produced and controlled in accordance with the agreed principles of GMP and quality standards, and to enhance the competitiveness of the manufacturers as well as consumers' confidence in their products. It also reduces costs of testing and certification process.[115]

3.2.6 Bilateral regulatory cooperation

Bilateral regulatory cooperation has also been sought in the pharmaceuticals sector. In particular, the mutual recognition agreements (MRAs) between the European Union and

113. It is based on the number of new pharmaceuticals launched in 1996 and the cost for pre-clinical testing. 1998 savings, which were in French Francs, have been converted to Euros at the rate of FRF 6.56 per EUR.

114. Alberto Grignolo (2010), "Expanding Global Pharmaceutical Harmonization: a look at PPWG and PANDRH", *Regulatory Focus* (March 2010).

115. ASEAN Secretariat (2009), "Fact Sheet: Ensuring Safe Pharmaceutical Products in ASEAN", (*www.aseansec.org/Fact%20Sheet/AEC/2009-AEC-026.pdf*).

third countries[116] typically include GMP sectoral annexes, under which each party recognises the conclusion of the GMP compliance programme carried out by the other party and the relevant certificates of the manufacturer. It is intended to bring benefits such as the reduction of approval costs, elimination or reduction of duplicate testing or enabling faster and more predictable access to foreign markets (European Commission, 2004).

There are a number of other forms of bilateral regulatory cooperation.[117] For example, EU and US authorities have agreed to such projects as joint inspections of companies that manufacture pharmaceuticals in the United States and in the European Union and of companies manufacturing active pharmaceutical ingredients in third countries. Another is to promote the exchange of inspection schedules, results, and information on inspected manufacturing sites in order to attain wider GMP inspection coverage collectively and to better identify manufacturing sites producing active pharmaceutical ingredients in third countries.[118]

3.2.7 Regulatory initiatives

Globalisation has become an important underlying consideration for regulatory initiatives in OECD members. On one hand, globalisation of manufacturing and R&D processes of pharmaceutical products has made it an important issue to ensure compliance of these processes taking place overseas with the domestic regulation. On the other hand, globalisation of these processes has added another cause to improve efficiency of the domestic regulation in order to foster domestic innovative activities to compete internationally.[119]

The US FDA has established its overseas offices since 2008 in China (Beijing, Guangzhou and Shanghai), India (New Delhi and Mumbai), Europe and Latin America to (a) establish relationships with US agencies located overseas and foreign stakeholders, including regulatory counterparts and industry, (2) gather better information locally on product manufacturing and transport to US ports, (3) improve the FDA's capacity to conduct foreign inspections, and (4) provide assistance to build the capacity of counterpart agencies to better ensure the safety of the products manufactured and exported from their countries (US GAO, 2010).

The European Union is in the process of reviewing its Clinical Trials Directive in response to criticism that the Directive "has lead to a significant decline of the

116. The MRAs on GMP are in operation with Australia, Canada, Japan, New Zealand and Switzerland.

117. *See* US FDA, *Memoranda of Understanding and Other Cooperative Arrangements*, at *www.fda.gov/InternationalPrograms/Agreements/MemorandaofUnderstanding/default.htm.*

118. European Commission, European Medicines Agency and US Food and Drug Administration, *Medicines Regulation: Transatlantic Administrative Simplification Action Plan* (June 2008).

119. Aside from the examples in the EU and Japan on pharmaceuticals, US FDA has announced its plan to improve the review process for medical devices in order to bring about "a smarter medical device program that supports innovation, keeps jobs here at home, and brings important, safe, and effective technologies to patients quickly". FDA New release, 19 January 2011. (www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm240418.htm)

attractiveness of patient-oriented research and related studies in the European Union, which greatly reduces competitiveness in Europe in the field of clinical research thus having a negative impact on the development of new and innovative treatments and medicines," (European Commission, 2009b). Alongside this international competitiveness concern, ensuring compliance with GCP, in particular fundamental ethical rules, in clinical trials performed in third countries is another key issue (*ibid*).

Japan has also taken initiatives to revitalise clinical trials in Japan, including the amendment of its GCP in 2007, under the successive multi-year plans for clinical trial activation. Such initiatives are expected to foster its innovative capacity, countering "hollowing-out" of clinical testing in Japan and facilitating participation in international clinical trials, and improve access to the latest pharmaceutical products marketed elsewhere (resolving "drug lag").[120]

Finally, other sector specific measures that concern pricing policy and reimbursement policy of pharmaceuticals have to date been left to the purview of each country. Even though these have not been addressed by the trade policy community, these policies can have consequences on trade flows. First, price differentials across countries encourage parallel trade, especially within the EU markets (OECD, 2008b).[121] Second, price levels of one country may affect price levels of other countries, either through international benchmarking for drug pricing or by market forces including parallel trade. Evidence suggests that the launch of new drugs may be delayed, if at all, in low price countries, possibly as an impact of the potential for low prices to spill over into other markets or incite parallel trade (OECD, 2008b). Moreover, price controls reduces the probability of a product to be introduced to the market, even after controlling for other country-level factors including the price levels (Kyle, 2007; OECD, 2008b). Despite the increasing awareness of such possible impact of pricing policy on trade flows and marketing decisions, they have not surfaced onto trade policy agenda.[122]

3.3 Intellectual property (IP)

3.3.1 Intellectual property in the pharmaceuticals sector

The central role played by patents in the pharmaceuticals sector is widely recognised.[123] Survey results consistently show the pharmaceutical industry to be one in which the greatest stress is placed on patent protection (Scherer, 2000; Cohen *et al*. 2000, Table 1).[124] Unlike most other industries, much of R&D expenditure in pharmaceuticals is

120. Ministry of Health, Labour an Welfare and Ministry of Education, Culture, Sports, Science and Technology, Government of Japan (2007), *New Five-year Plan for Clinical Trials Activation* (30 March 2007, in Japanese); Cabinet Decision (2010), *The New Growth Strategy: Blueprint for Revitalizing Japan* (18 June 2010).

121. Andrew Jack, "European drug groups fear parallel trade", *FT.com* (7 June 2010).

122. The EU has adopted "Transparency Directive" (89/105/EEC) in 1989 to ensure transparency of pricing and reimbursement measures of the Member States, so that these measures would not create obstacles to the internal market. A review of this legislation is now under discussion as a part of the initiative to enhance international competitiveness of EU industry. *See* European Commission (2010).

123. Cockburn (2009, pp. 152-55) points out that other intellectual property rights, such as trademarks and copyright, are also important for the sector.

124. *See also* Ernst & Young (2010b) pp. 68-69 (contrasting drug and IT companies).

on discovery of promising molecules. Without a patent or other protection, an imitator could free-ride on the information created by the innovator's R&D investment. By making a comparatively small investment for the necessary process engineering, a rival could use such information to enter the market as a competitor (Scherer, 2000). At the same time, technological developments have made it easier to specify and communicate technological know-how in the pharmaceuticals and chemicals sector. It is very difficult to invent around a patent on a drug, since a slight change in the underlying gene sequence of a protein can result in very different functions. It is also possible to patent particular molecules, building blocks for product innovation (Anand and Khanna, 2000).

The salience of the patent regime in this sector is such that it can change the industry and the market. For example, patent protection for a genetically modified microorganism laid the foundation for the birth of the biotechnology industry[125] (Laforgia *et al*., 2007; PwC, 2010a). Seemingly subtle technicalities of implementation can determine important industry characteristics. Aoki *et al*. (2006) attribute the large number of "me-too" drugs in Japan in the 1970s-1980s to the narrow scope of patent claims, a practice that lasted until 1995, coupled with the national health insurance scheme and drug approval system. Moreover, transformation of the pharmaceuticals industry in emerging economies, such as India, is underway since the introduction of the product patent.

Much attention has been paid to optimising the balance between providing adequate protection for new products and encouraging their widespread use (Tarabusi and Vickery, 1995). There have been a number of empirical studies on the economic impact of intellectual property,[126] and a subset of studies has focused specifically on pharmaceuticals.[127] First, Lanjouw (2005) shows that stronger patent protection, alongside less stringent price control, tends to encourage more or faster launches of drugs. The results are clearer among high income countries, but the estimation results show that these variables are broadly relevant among low and middle income countries. Second, R&D activities can be induced by patent protection, as shown in some country-specific studies (Cockburn, 2009). A cross country study (Qian, 2007) shows that the implementation of pharmaceutical patent laws alone does not promptly stimulate domestic pharmaceutical innovation, but national patent laws in combination with levels of income, education and economic freedom do have a positive effect on pharmaceutical innovation. Another cross country study on the location of clinical trial sites point to at least correlation with patent protection (Cockburn, 2009).[128]

Beyond promoting domestic R&D, patent protection plays a role in facilitating and governing transactions in technology, although it is difficult to test this directly (Cockburn, 2009. Instead, several studies have approached various channels of technology transfer. On the impact on FDI in pharmaceuticals, Qian (2010) shows that,

125. Diamond v. Chakrabarty, United States Supreme Court (16 June 1980).

126. *See* Jaffe (2000) for a survey of literature. *See also* Cavazos and Lippoldt (2010).

127. *See* Cockburn (2009) for a literature survey, which the remaining part of this paragraph draws on.

128. In contrast, Linton and Corrado (2007, pp. 175-76) refer to the increasingly sophisticated R&D projects in India despite the reported inadequacies in patent law and explain that IP protection works differently in R&D projects than in the case of product patenting and commercialisation. Confidentiality of proprietary data in R&D projects is protected by the relationship between the parties, their contract and compliance with international information security management standards and domestic contract law.

similarly to Qian (2007), implementation of pharmaceutical patent protection in combination with economic freedom and education, rather than on its own, works to attract FDI. It also shows that such implementation itself induces pharmaceutical imports, another channel of technology transfer.[129] Patent protection can facilitate cross-border cooperation in R&D. Bennato and Magazzini (2009) find that the index of IPR protection exerts a positive effect on cross-border collaboration in pharmaceutical patent. Moreover, Magazzini *et al*. (2009) argue that disclosure of information through patents enables firms to monitor the competitors' R&D activities and thereby encourages innovative efforts and stimulates competition within the industry.

It should also be noted that some studies have raised the concerns that proliferation of patents may at some point "choke" biomedical innovation by raising transaction costs, though the empirical evidence on this is mixed (Cockburn, 2009).[130] Nonetheless, from the literature it is clear that the treatment of intellectual property is a real issue in the context of collaboration in drug discovery. Practitioners emphasise the role of patents in giving incentives to participate in collaborative work in the long run, and the need to work out the risks and rewards of such collaboration before starting the partnership.[131]

Thus, a number of studies point to the positive role of patent protection in promoting innovation as well as international transfer and cooperation in technology, although it should be borne in mind that each study carries its own nuances and limitations.[132]

3.3.2 Developments after the TRIPS Agreement

The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), one of the WTO agreements, has had critical implications for the pharmaceuticals sector. In particular, for many developing countries where product protection was not available for pharmaceuticals,[133] this has meant in practice the introduction of pharmaceutical product patents by 2005, though with an extended transition period for LDCs (Articles 27.1, 33 and 65.4).

129. Ivus (2010) shows that the TRIPS Agreement substantially boosted patent-sensitive exports (including pharmaceuticals) from developed countries to developing countries.

130. In addition to articles reviewed in Cockburn (2009), a case study on Human Genome Project by Williams (2010) documents an incident where exercise of IP rights concerning the human genome led to substantial reductions in subsequent scientific research and product development outcomes. Murray *et al*. (2009) highlights reductions in the diversity of experimentation that follows from a single idea as a neglected cost of IP. In contrast, Cohen and Walsh (2007) argue that secrecy is a more frequently employed means of exclusion of others and control over materials and that patents are a less effective means of exclusion.

131. "Harnessing open innovation", *Nature Reviews*| *Drug Discovery* (May 2009); Patrice Talaga (2009), "Open Innovation: share or die …", *Drug Discovery Today*, Volume 14, Numbers21/22 (November 2009).

132. Cockburn (2009) emphasises limitation in data, need for adequately controlling other factors and inherent difficulty to observe the linkage in aggregate data, as well as lack of comprehensive indicator that represents the strength of pharmaceutical IPRs.

133. These countries included Argentina, Brazil, Cuba, Egypt, India, Kuwait, Morocco, Pakistan, Paraguay, Tunisia, Turkey, United Arab Emirates and Uruguay. Most new members to the WTO have agreed to apply the agreement at the time of their accession.

A survey covering pharmaceutical companies in the Asia Pacific region shows that intellectual property protection has been a key concern for the industry (PwC, 2007b). Some 63% of multinationals (MNCs) agree that generics' failure to respect intellectual property negatively affects MNC sales and market share and 60% say that lack of intellectual property protection is a major deterrent to investment, concerns which are echoed by the domestic innovative drug companies as well (56% and 45%, respectively). TRIPS implementation is helping to address this situation and has generally resulted in significant strengthening of patent protection (Ivus, 2010).

Despite substantial improvement made in patent protection in the emerging markets in recent years, various challenges remain. For example, Linton and Corrado (2008) cite lack of clarity in data protection[134] and exclusion from patentability for derivatives of known substances[135] as two remaining gaps in Indian patent legislation. Anderson *et al*. (2009) report that the major challenge in India is the issuing of patents, whereas it is the waiting period of about two years for patent review and approval in Brazil, and that, in China, enforcement of patents after being granted is the major problem. The monitoring reports by the European Commission and the US Government also list such issues as lack of effective protection of data generated to obtain marketing approval, lengthy and difficult patent registration process and counterfeiting (regarding patents and trademarks), specifically or especially in pharmaceuticals, in some emerging economies (European Commission, 2009c; USTR, 2010). They both note on-going bilateral dialogue or bilateral agreements with major players as part of their efforts to address the issues of IP protection.

Finally, an issue that has been much discussed in relation to pharmaceuticals has been the possibility that a WTO member "allows for other use of the subject matter of a patent without the authorization of the right holder" (TRIPS Article 31.1);[136] known as "compulsory licensing", this is a process that is subject to a number of conditions aimed at protecting the legitimate interests of the patent holder (e.g. appropriate compensation is required). The Agreement envisages that "any such use shall be authorized predominantly for the supply of the domestic market of the Member authorizing such use" (Article 31.1.[f]). This poses a problem for countries without production capacity and having a demonstrated need to import drugs. WTO members have adopted provisions aiming to overcome such legal problems, and they were translated into the 2005 amendment to the TRIPS Agreement. This amendment enters into effect when two thirds of members accept it, a result that is not yet attained.[137] This new scheme has been used only once, and is still a subject of considerable debate from the viewpoint of access to medicine by developing countries.[138]

134. Article 39.3 of TRIPS Agreement stipulates that the undisclosed data submitted for marketing approval shall be protected "against unfair commercial use".

135. Patent Act of 2005 contains an exception to patentability if the discovery "does not result in the enhancement of the known efficacy". *See e.g*. Ram (2006, p. 199); A. Nair, "Report from India", PharmTech.com (2 November 2010).

136. The description in this paragraph draws on WTO (2006).

137. *See* Kennedy (2010) for a background to the current state of acceptance.

138. *See* WTO (2010), *Little-used 'Par.6' system will have its day, WHO tells intellectual property and health review*, 2010 News Items (26 and 27 October 2010).

IV. Conclusions

Trade and innovation linkages

Various linkages between trade and innovation are highlighted in this paper. First, global sales have always been an important source of revenue for large pharmaceutical companies, and the revenues from global sales have provided incentives and funds for R&D investment for future innovation. Global sales of pharmaceutical products, in turn, mean global diffusion of advanced medical technology and benefit importers in terms of improved health status, an essential basis for future growth and innovative capacity.

Whereas competitive pressure from new in-patent substitutes as well as generic drugs are putting pressures on profitability of pharmaceutical companies, and globalisation is providing new sources of innovation. More clinical trials are being carried out in emerging economies, and R&D activities are becoming more globalised. Organisational innovation has been taking place to improve performance of global R&D activities. Growth of emerging markets is providing new opportunities of global sales for pharmaceutical companies, and challenges to devise innovative marketing methods to penetrate non-traditional markets. M&As involving emerging markets are gaining ground, in order to secure a foothold in these markets as well as to enhance R&D collaboration. From the side of the companies in emerging economies, M&As are an instrument to transfer skills and technologies to foster innovative capacity as well as to capture market opportunities.

The state of R&D

In the pharmaceuticals sector, product innovation is the cornerstone to generate health benefits and financial reward and involves a uniquely long and costly process. It is closely interwoven with sector specific regulatory regimes, including product approvals, pricing policy and healthcare coverage and reimbursement. Patent protection also plays a critical role in this sector. It typically takes more than 10 years to bring a drug to the market, costing about USD 1 billion on average. Only one in 5 000 to 10 000 investigational compounds ever makes it to the market. Production and R&D activities are concentrated in the United States, Europe and Japan.

Currently, this sector is in substantial transition. There has been an intensification of competition due to faster entry of substitutes (competition with in-patent drugs) and increasing penetration of generic drugs. Competition with generics will intensify as patent protection for drugs that account for a large proportion of current revenues is expiring over the next few years. Moreover, the rising cost of healthcare is an increasingly pressing issue in many developed countries, putting downward pressure on drug prices.

Further product innovation is even more essential under such circumstances, but there has also been a widespread concern that R&D productivity may be declining rather than improving. Increasing R&D expenditure has not translated into an increasing number of new drugs, and the cost of new drug development is seen to be rising rapidly. Recent estimates are mixed about whether current R&D projects cover the cost of finance, and many largest pharmaceutical companies may not have pipelines sufficiently valuable to offset the loss of revenue due to the imminent expiration of patents.

The state of globalisation

Foreign sales have occupied a large proportion of global sales for many pharmaceutical companies (30-35% for US companies and even more for European companies), contributing to high growth and profitability since the 1980s. Empirical evidence shows that current profitability is a strong determinant of R&D activities in the pharmaceuticals sector by providing incentives and funding for R&D investment. These suggest that exports have been among the essential factors to foster product innovation in pharmaceuticals.

Exports of pharmaceutical products have also meant diffusion of medical technology generated by exporting countries, thereby benefiting the importing countries in terms of improved health. A statistical analysis suggests that the countries at the 25th percentile and at the 75th percentile in terms of medical imports per capita have a difference in life expectancy of about 3.5 years, holding other variables constant. Some economic and bioscience literature further suggests that improved health status can serve as basis for a long term growth by way of human capital accumulation and technological progress.

Around 80% of world trade has been taking place between high income countries, and most of the top 20 exporters are OECD members, yet emerging economies are gaining weight as markets, locations for R&D and production, and actors in M&As. Although mature markets such as the United States, Europe and Japan still hold a dominant proportion of global sales, one third of annual global sales growth are already being generated in the emerging economies. Large pharmaceutical companies are actively engaging in M&As in emerging economies, in an effort to gain a foothold in these markets as well as to establish R&D collaboration in these countries. Some companies in emerging economies, most notably India, are also engaging in outward acquisition in an effort to capture market opportunities in developed countries as well as to acquire skills and technologies.

In order to reduce the cost of drug development, more clinical trials are being carried out in emerging economies, which have earned a reputation as locations to provide faster services at a lower cost in clinical trials. Improvement in intellectual property protection in those countries, due to implementation of the TRIPS Agreement, has also contributed to opening up this opportunity. Established pharmaceutical companies are also conducting R&D activities outside of their home country. In the case of US companies, although most of such R&D is done in Western Europe, Japan and Canada, R&D in emerging economies has been expanding rapidly for the past few years. Some pharmaceutical companies have moved to redesign their R&D departments to better manage the global R&D activities.

Trade policy issues

Thus, global business activities have been a feature in this sector, and it is entering a new phase with the entry of the emerging economies. Given this, various kinds of trade facilitating measures, *i.e*. tariff liberalisation, regulatory co-operation and intellectual property protection, are already in place. Most of the OECD members have bound their tariffs at zero for pharmaceutical products as a result of the Uruguay Round, and imports of pharmaceuticals to these countries are now essentially duty free. However, substantial tariffs remain in other countries, and a proposal for further tariff elimination in a range of healthcare products, including pharmaceuticals, has been tabled in the current DDA negotiations.

Reflecting the unique regulatory regime in this sector, a number of plurilateral and bilateral initiatives to address regulatory issues have been taking place, going beyond the disciplines under the WTO's TBT Agreement, and considerable progress has been made in regulatory harmonisation, mutual recognition and enforcement cooperation. Over 50 guidelines to harmonise regulations have been completed under the ICH in such categories as quality, safety and efficacy of pharmaceuticals, which have been implemented in the participating regions (the European Union, Japan and the United States). PIC/S has been promoting common GMP standards, and the OECD's implementation of the Mutual Acceptance of Data (MAD) system reduces duplicative testing.

The entry of emerging economies in this sector is providing new challenges as well as opportunities. Since the existing plurilateral arrangements were initiated by major players with an established pharmaceutical industry, partnership with the emerging economies is being sought in each forum in order to extend the geographical reach of the impact of these instruments. Moreover, the globalisation of manufacturing and R&D processes by multinationals, ensuring their compliance with the domestic regulatory standards, such as GCP and GMP, has become a pressing issue. Many emerging economies, for their part, are seeking to adapt to the international standards with a view to establish the credibility and the competitiveness of the industry, but a gap still remains. Regulatory cooperation involving emerging economies is likely to become more important to ensure compliance while facilitating trade and globalisation of R&D. In addition, globalisation has created an opportunity to take a fresh look at the efficiency of the regulatory regime in order to maintain innovative activities and industrial competitiveness.

Intellectual property, most notably patents, is of critical importance for this sector. While there have been considerable concerns about the state of patent protection in some emerging economies, the situation has been significantly improving due to the TRIPS Agreement, particularly the introduction of product patents for pharmaceuticals. Concerns remain, however, regarding the actual implementation of the patent regime in several emerging economies, and bilateral dialogues are being pursued between major players.

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