



The pharmaceutical industry, innovation, generics and competitiveness in the context of EU Enlargement

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Summary

The market of medicines in new members of European Union with population of 75 million people totaled in € 7 billions. The product patents were implemented during 1990's in these countries. Patent protection is a key concern for research – based industry in unified market. In central and Eastern European markets the generics make about 70% of all medicines prescribed. The novelty on the market are “authorized generics”.

Key words:

generics, pharmaceutical's market, EU accession countries, intellectual property.

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The European Union (EU) healthcare industry is the second largest in the world following North America. New EU countries are expected investment heavily in healthcare. These EU countries are trying hard to raise their healthcare standards to meet EU health regulations. The first few years of accession are likely to result in a rising Gross National Product (GNP) and a sharp increase in risks to public health. The drive now is for new member countries to put into operation long-term, sustainable systematic changes in their respective healthcare systems. The present size of the pharmaceutical markets of the countries undergoing EU accession is approximately € 7.0 billions (1).

All new medicines introduced on the market are the result of lengthy, costly and risky research and development conducted by pharmaceutical companies. The development process of medicine constituting a real innovation in therapy takes seven to eight years and costs around € 100-300 million. The latest data estimate the average cost for a new chemical or biological entity as a medicine at € 850 million. According to the above, we may divide the pharmaceutical industry into two worlds: The first one includes innovative medicines, original ones, introduced into the market for the first time, whose creation entails enormous financial outlay. The second one, includes generic medicines, counterparts of those innovative medicines whose patent protection has expired.

A generic medicinal product shall mean a medicinal product which has the same qualitative and quantitative composition of active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters or derivatives of an authorized active substance must be supplied by the applicant. The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form. Bioavailability studies are required of the applicant if they can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines (12).

Generics are considerably less expensive than the original medicine, because their manufacturers do not incur the risks and costs associated with the research and development of innovative medicines. Before they reach pharmacies, their values have to be proved through testing, but preclinical tests and clinical trials can be replaced by bioequivalence studies .

Only 15% of drugs approved from 1989 – 2000 were Highly Innovative New Medical Entities. Of the TOP50 new chemical entities (NCEs) introduced since 1980, only 16 originated in Europe, compared to 24 in the United States. (Fig. 1).

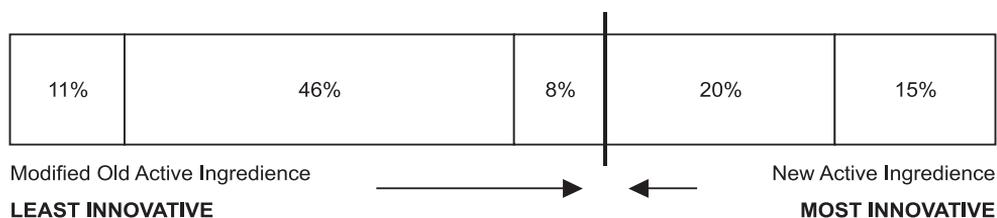


Fig. 1. Innovative Medical Entities; explanatory: 11% – no clinical improvement; 46% – no significant clinical improvement; 8% – clinical improvement; 20% – no significant clinical improvement; 15% – clinical improvement. Source: NIHCM Report – FDA Data 2001.

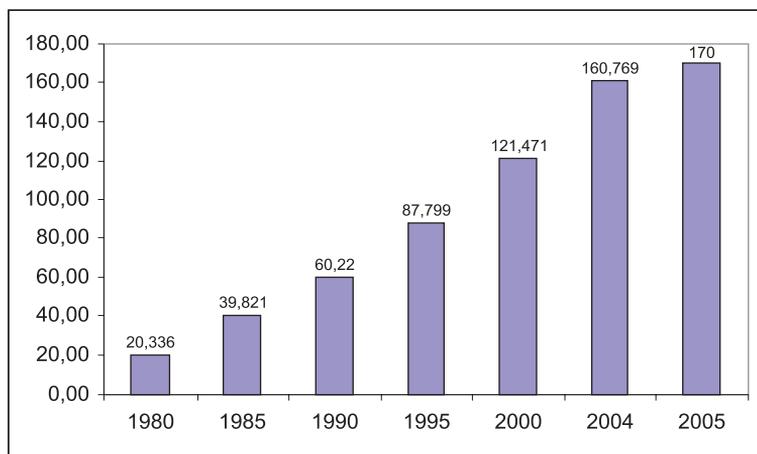


Fig. 2. European pharmaceutical production, 1980-2005 (€ mln). Source: EFPIA member associations (21).

On May 1st 2004, the European Union experienced the largest expansion in its history, adding 10 new members with 75 million people, giving the EU a total of 25 member states, 20 official languages, a population of 450 million, and a combined GDP of 9.3 trillion euros. Except Cyprus and Malta, all of the incoming countries are former members of the Communist block. Although the incoming countries increased the EU population by 20 percent, they added only 6 percent to current EU pharmaceutical sales. With per capita incomes averaging only 22 percent of the level for the 15 pre-expansion states and drug prices that are 25 to 30 percent lower, it will be some time before pharmaceutical consumption catches up to current EU levels. The European Commission says that it may take up to 40 years for income levels to reach parity throughout the Union. All of this, combined with the intellectual property considerations, means that expansion is likely to have a generally negative impact for at least the next decade (2). (Fig. 2).

In contrast to the subdued growth in the pharmaceutical markets of the former 15-state European Union, pharmaceutical markets in the “new” EU accession markets are expanding vibrantly. While the former has been increasing at 8% per year, the latter has been growing at 16.5% per year over the past five years. The pharmaceutical market in the new EU countries represents about 8% of the EU15 market (3). Propelled by the twin advantages of low costs and easy patient recruitment, the new EU also offers tremendous scope for conducting clinical trials (3).

Europe is the main manufacturing and research location for human-use vaccines. About 90% of the total production of the worldwide vaccine manufacturers originated from Europe in 2004. Simultaneously, in terms of market sales, North America is the leading market accounting for nearly half of the value of worldwide vaccine sales (which was estimated at € 6.250.3 million in 2004). The number of R&D pro-

jects (from pre-clinical stage to Phase III development) by major international vaccine manufacturers amounted to a total of 123 as of 31 December 2004. About two thirds of the total number of R&D projects were located in Europe (Europe: 79 projects, North America: 43 projects, Other countries: 1 project). Major international vaccine manufacturers altogether had 19 manufacturing sites and 16 R&D sites based in Europe in 2004 (4). (Table 1, Fig. 3).

Table 1

Number of locations of manufacturing and R&D sites by international vaccine manufacturers in Europe

| | Manufacturing | R&D |
|-----------------------|----------------------|----------------|
| Total | 19 | 16 |
| Germany | 2 | 2 |
| Austria | 1 | 1 |
| Belgium | 4 | 4 |
| France | 2 | 2 |
| Italy | 2 | 2 |
| Netherlands | 1 | 2 |
| Spain | 1 | – |
| Switzerland | 2 | 2 |
| U.K. | 1 | – |
| Czech Republic | 1 | – |
| Hungary | 1 | 1 |

Source: European Vaccine Manufacturers (EVM), 2006

In 2004 EFPIA countries' pharmaceutical exports totalled € 165,000 million. Exports to non-EU countries amounted to € 62,300, i.e. 37,7% of total exports. The EU's main trading partners are the USA and Switzerland, with the USA being an increasing exporter of medicaments to Europe (4). (Fig. 3).

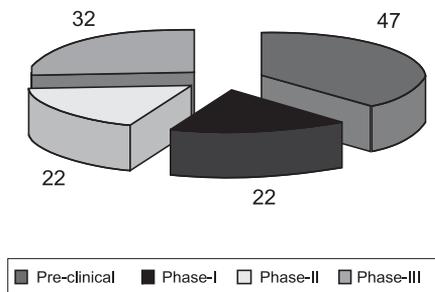


Fig. 3. Total number of R&D projects by international vaccine manufacturers. Source: European Vaccine Manufacturers (EVM), 2006 (22).

Until the mid-20th century, patents in Europe covered the manufacturing processes, not the product. Process patents are easily circumvented by making minor manufacturing changes and therefore are not a sufficient means of protecting the investment required for the development of new drugs. In 1949, the United Kingdom became the first European country to extend patent protection to products, and over the next five decades as other European states followed the UK's lead, product patents became an established part of EU law.

There is another important difference between the 8 other new EU member states and Cyprus and Malta. The latter are both former colonies of the United Kingdom. On achieving independence, in 1960 and 1964 respectively, they based their own legal systems on existing UK law. Their intellectual property regime was deemed sufficiently close to that of current EU members. Additionally, the Cypriot and Maltese pharmaceutical industries are too small to pose a major threat.

Until the 1990's, in eight of the ten new Member States only manufacturing process patents were granted. Finally during the 1990's, these countries implemented product patents. All of the expansion states now offer product patents, but because the laws were introduced recently, many pharmaceutical products that were developed in the early 1990's and before have no patent protection in these countries (2). (Table 2).

Table 2

Date Product Patents were Introduced in EU Accession Countries

| Country | Year of Introduction |
|-----------------|----------------------|
| Czech Republic | 1991 |
| Slovak Republic | 1991 |
| Latvia | 1993 |
| Poland | 1992 |
| Slovenia | 1993 |
| Estonia | 1994 |
| Hungary | 1994 |
| Lithuania | 1994 |

Source: PPR Communications

More recently, the countries of the European Union have extended pharmaceutical-specific forms of intellectual property protection such as data exclusivity and Supplemental Protection Certificates (SPCs) (2).

“The European Generic medicines Association (EGA) understands and fully supports the basic principles of the proposed *Directive of the European Parliament and of the Council on measures and procedures to ensure the enforcement of intellectual property*

rights, which is the prevention of counterfeiting and piracy. However the European generic medicines industry has major concerns that the measures provided to enforce Intellectual Property rights might be misapplied and misused by IP holders against legitimate competition as well as have undesired effects on innocent parties. Concerning the safeguard clauses introduced by the proposed Directive in order to protect innocent defendants from abusive litigation, the EGA is concerned that these are not in fact achieving the right balance.

With respect to the scope envisaged for the proposed Directive, a fundamental difficulty concerns the separation between piracy and counterfeiting on one hand, and other intellectual property rights infringements on the other [...]” (5).

The key principle underlying the legal framework of accession is that all EU legislation (*acquis communautaire*) automatically becomes part of the national law of the new member states. In essence, therefore, the acceding countries have accepted the existing EU legislation and any rights established prior to the date of accession (6).

On 26th of March, 2001 the European Commission established the High Level Group on Innovation and the Provisions of Medicines (also known as the G10 Medicines). The Group’s mandate was to propose a new agenda to improve the framework for competitiveness in the pharmaceutical industry and to harness its power to deliver on Europe’s health-care goals (7).

Solutions for protecting the pharmaceutical industry are, in part, the result of experience gained through the 1986 EU accessions of Spain and Portugal. Following a six-year transition period, both introduced product patents in 1992, but they provided no retroactive protection of any kind. Had the “free movement of goods” principle been extended to allow the import of low-cost generics from these markets to other member states, it would have largely negated the value of the patent in Europe. To prevent this, the EU permitted patents issued elsewhere at a time when they were not available in Spain or Portugal (before 1992) to block parallel trade for a period of three years. It was believed that by the end of 1995, Spanish and Portuguese prices would rise to near the European average, eliminating the economic incentive for parallel trade. Although prices did rise, the three-year period was not sufficient to close the gap, and parallel traders quickly moved to exploit the opportunity as soon as the import ban lapsed. More than ten years after the introduction of product patents, Spain’s prices still average only 62% of the United Kingdom’s. After this experience, the research-based industry was committed to finding a more effective means of protecting the value of its intellectual property.

The presence or lack of product patents is just one of the factors affecting the price of drugs in a market. The country’s relative level of wealth and government-imposed price controls are at least as important and can serve to depress prices irrespective of the intellectual property regime (2). Process patents issued before patent laws were changed remain in force in the accession countries, irrespective of whether product patents exist in current EU member states. In other words, the introduction of product patent laws in the candidate countries had no retroac-

tive effect on products that entered the market before the introduction of more effective intellectual property (IP) legislation. Patent protection thus remains a key concern for the research-based industry, not least because goods not protected by a derogation are supposed to circulate freely in the unified market (8). Due to understandable tensions between manufacturers and importers, there are numerous complex issues involved concerning intellectual property, competition law and regulatory matters. For detailed rules one must refer to European Court of Justice case law and the European Commission guidelines on regulating and interpreting parallel trade. Some problems remain unresolved (9).

The size of the generic market differs widely in the various EU member states. The differences are mainly a consequence of the different policies followed by the member states. Among the main factors affecting the size of the generic market are:

- market conditions for new medicine,
- pricing/reimbursement structures,
- prescribing/dispensing traditions,
- requirements,
- the existence of specific incentives to encourage generic use (10).

Penetration of generic medicines is more successful in countries that permit (relatively) free pricing of medicines (Germany, United Kingdom) than in countries that have pricing regulation (Belgium, Italy, Spain). This is because countries that adhere to free market pricing generally have higher medicine prices, thereby facilitating market entry of generic medicines, and a higher price difference between originator and generic medicines (11). The situation is significantly different in many Central and Eastern European countries, where generics make up as much as 70% of all medicines prescribed in terms of volume, whilst in value terms generics represent only 30% of pharmaceutical expenditure. Consequently, the availability of affordable generic medicines in these countries, many of which joined the EU on May 1st 2004, is actually a major budgetary factor in both the retail and hospital sectors (13). To analyse the European generic markets it is important to understand the core nature of national regulations on pharmaceutical products. They reflect the overall underlying national attitudes towards the provisions and financing of healthcare. The national regulations operating in a given market determine the structure and the environment, in which generic manufacturers need to function, commercialize and compete (14). Generics make up the majority of the new countries' products, accounting for 60 percent of prescription volume in the Czech Republic, 70 percent in Hungary, and 77 percent in Poland. Branded generics are particularly popular, as they offer the dual benefits of lower prices and higher perceived quality. Because of the evolution of patent law, the "generics" category often includes products that are patented elsewhere (2). (Table 3).

Table 3

Pharmaceutical market value (at ex-factory prices)

| EFPIA 2004 | € Million |
|----------------|----------------|
| TOTAL | 120.007 |
| Germany | 21.551 |
| Czech Republic | 1.163 |
| Hungary | 1.556 |
| Poland | 2.939 |
| Slovakia | 487 |
| Slovenia | 413 |

Source: EFPIA member associations (official figures) – Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Slovakia, Slovenia: data supplied by IMS Health

The experience of European countries shows that there is no single approach towards developing a generic medicines market. For instance, demand for generic medicines in mature markets is driven via generic substitution by pharmacists in Denmark and the Netherlands, a favourable attitude of physicians towards generic medicines in Poland, physician budgets in Germany and United Kingdom. Also, the development of a generic medicine market needs to be actively sustained by a generic medicine policy. Consequently, countries that have promoted generic medicines for 10-15 years naturally have a more mature generic medicines market than countries that have only recently implemented measures to stimulate generic medicine use (15).

Compared with patents, the market power of data exclusivity is, in theory, less restrictive, mainly because it does not legally prevent other companies from generating their own registration data. However, in practice, the vast financial resources and extended time required for gathering and generating pharmaceutical registration data for a new drug create a market barrier that is too high for generic-based companies (16).

The new EU legislation for pharmaceuticals:

- Encourages generic R&D before patent expiry.
- Allows marketing of generics where branded pharmaceuticals have been withdrawn for commercial reasons.
- Provides a more efficient system for the registration of generic medicines (new Decentralised System).
- Ensures greater harmony between newly approved generic medicines and older approved brand equivalents.
- Provides clear scientific and legal definitions of generic and biosimilar medicines, which were actually lacking in EU law.

While this legislation may simplify the registration of generics and promote increased manufacturing of generics in the EU, the new law will increase the overall period of time that generic manufacturers must wait before registering their products (13).

Patents and data exclusivity may be treated as two separate forms of intellectual property. Patents are granted to the inventions and innovations embodied in a new medicine. Data exclusivity, on the other hand, is an expression of trade secrets. It is aimed at protecting and safeguarding the proprietary know-how and information included in the registration files against any type of unfair commercial use (16).

A key question is whether the protection under the Official Secrets Acts in different countries provides appropriate and adequate protection to originators for their proprietary test data and whether they mandate the governments not to disclose or rely on the proprietary data for the marketing approval of “generic” (“follower”) copies of the pharmaceutical products without the explicit approval of the originator, at least for a reasonable period. Another point to be debated is whether the countries, which tend to trust the Official Secrets Acts to provide the necessary protection, have built in mechanisms within the meaning of such Acts, for the originators to enforce their rights for the proprietary test data (17).

The distinction between patents and data exclusivity as an expression of trade secrets (or undisclosed information) is based, *inter alia*, on the provisions of NAFTA (Art. 1711) and the TRIPS agreements (Article 70.9 “Exclusive Marketing Rights”, Article 39 – protection of undisclosed information).

With respect to the distribution of goods within the EU, the rule is that once the owner of IP rights has marketed or given his/her consent to market his/her goods, it is no longer possible to prevent a third party from selling, marketing, importing or exporting those goods within the EU (20).

Basic principle: free movement of goods (FMGO) within the Community (i.e. EU EEA countries):

- Article 28 EC Treaty: no artificial barriers to trade between MS;
- Article 30 EC Treaty: unless justified by reasons of protection of i.e. intellectual property rights.

By the end of 2004 some 35% of top selling pharmaceuticals had been patent expired, creating a major opportunity over the next few years for increasing generic medicine sales, both in the community prescription and hospital sectors.

According to EGA opinion: “Generic competition drives pharmaceutical innovation”. Only impending patent expiry and generic competition can create the market conditions required to stimulate pharmaceutical innovation (18).

Recently, however, research-based pharmaceutical companies, such as Pfizer, Merck and Eli Lilly have begun to retaliate against generic companies that challenge their patents by adopting the strategy of „authorized generics“. This strategy aims to nullify the substantial prospective profits of a generic company that has been granted 180 days marketing exclusivity (on the basis that it was the first to challenge the pat-

ent of the original drug) by granting another „friendly“ generic company a license to produce a generic substitute to the original drug (19). In other words, the strategy of authorised generics speeds up competition in the generic market, at the expense of the exclusivity period of both the originator and the generic company that was entitled to the 180 days of marketing exclusivity. However, although this strategy is clearly based on commercial interests, it is still positive from the point of view of the public, who can now enjoy a wider selection of generic drugs at lower prices.

Literature

1. Mahesh Sawant, 'New' EU countries: Huge potential, February 03, 2005, Pharmabiz.
2. Todd Clark, Growing Pains for pharma, the EU expansion won't pay off for at least a decade, Pharmaceutical Executive for global business and marketing leaders, May 2004.
3. Rita D'Aquino, Hot Spots in the pharmaceutical pipeline, Chemical Engineering Progress (CES), August 2005.
4. The pharmaceutical Industry in Figures, European Federation of Pharmaceutical Industries and Associations, 2006.
5. EGA Proposal for amendments concerning *Directive of the European Parliament and of the Council on measures and procedures to ensure the enforcement of intellectual property rights*, June 2003.
6. Constant van Nispen, The consequences of EU enlargement for the pharmaceutical sector, November 2003, Newsletter Pharma.
7. <http://pharmacos.eudra.org>
8. Boom or gloom for parallel trade in the enlarged EU?, 29 January 2004, <http://open.imshealth.com>
9. Marcin Tomasiak, Pharmaceutical Variations on a Theme, 15 March 2006, Warsaw voice, <http://www.warsawvoice.pl>
10. <http://www.euractiv.com/en/health/generic-medicines>
11. Magdalena Bartosik, Data Exclusivity-Protecting Original Medicinal Products, 15 June 2005, Warsaw voice, <http://www.warsawvoice.pl>
12. European revision offer new freedoms for generics, Generics Bulletin, 16 Januar 2004.
13. The role of generics in Europe, <http://www.egagenerics.com/gen-geneurope.htm>
14. A review on the European generic pharmaceutical market in 2005, EGA internal survey, 2005.
15. Steven Simoens, Sandra De Coster, Sustaining Generic Medicines – Markets in Europe, Research Centre for Pharmaceutical Care and Pharmaco-economics, Katholieke Universiteit Leuven, April 2006, Belgium.
16. Meir Perez PUGATCH, Intellectual property and pharmaceutical data exclusivity in the context of innovation and market access University of Haifa ICTSD-UNCTAD Dialogue on Ensuring Policy, Options for Affordable Access to Essential Medicines Bellagio, 12-16 October 2004.
17. Prabuddha Ganguli, Complying with Article 39 of TRIPS.. a myth or evolving reality, <http://www.ircc.iitb.ac.in>
18. National Institute for Health Care Management, May 2002, The European Generic medicines Association (EGA) "Making Medicines Affordable and Industry Competitive", EGA Fact Sheet No. 3.
19. Indian Infoline.Com. Norvasc...Pfizer's medicine, Dr. Reddy's poison (3 March 2004), <http://www.indiainfoline.com>
20. Cyra Nargolwalla, David-Irving Tayer and Laurence Vercaemer, Europe, SUPPLEMENT – Life Science Yearbook 2002, Cabinet Plasseraud, Paris.
21. European Federation of Pharmaceutical Industries and Associations, Today's Research, tomorrow's cures, The Pharmaceutical Industry in Figures, Key Data 2005 update, http://www.efpia.org/6_publ/infigures2005.pdf
22. Helena Tobin, Neil Turne,r Boom or gloom for parallel trade in the enlarged EU? IMS Health (19 February 2004), PPR Communications, http://pharmalicensing.com/articles/disp/1077220662_40351536b8660