European Union: Authorization and Registration of Pharmaceuticals

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Summary

Competencies in the pharmaceutical sector are shared between the Commission and Member States. Due to national budget responsibilities, two key issues, namely pricing and reimbursement levels, remain entirely with the Member States and can vary considerably. European Union-wide pharmaceutical legislation focuses on some aspects of marketing (e.g. packaging, labeling, and advertising), safety (e.g. pharmacovigilance inspections, Good Manufacturing Practices, and good clinical practices), transparency, and authorization procedures.

This report provides both an update on EU legislation of the sector and discusses an overview of issues affecting it, including the regulatory framework, EU enlargement, and competitiveness issues.

Authorization Procedures

EU-wide authorization for use can be obtained either under the "centralized procedure" or at the national level, under the "decentralized procedure"; in the latter case, the principle of "mutual recognition" between European Union Member States applies. The same procedures can be used for products typically considered to be prescription-based or over-the-counter because a product's EU classification is designated only when authorization is granted. As stated in article 8 of Directive 2001/83/EC, only organizations established in an EU country may apply for authorization. Therefore, American companies without an office in the European Union must contract with an entity established in the EU to act as their representative.

The new Regulation 726/2004 overhauling EU policies concerning the authorization of pharmaceuticals and establishing the European Medicines Agency (EMEA) became effective in October 2005. Based in London, the EMEA is charged with approving new pharmaceuticals under the centralized procedure and documenting the use of existing drugs from either procedure on the market, including any reported side effects or other difficulties. The centralized procedure provides one authorization for use that is valid throughout the EU. The centralized procedure is currently required to gain authorization for use for 1) all biotech pharmaceuticals, 2) pharmaceuticals with a newly created active substance used to treat AIDS, cancer, neurodegenerative disorders, and diabetes, and 3) designated "orphan" medical products. Since May 2008, drugs for auto-immune diseases, immune dysfunctions, and viral diseases must also be registered through the centralized procedure. After EMEA approval, the Commission normally grants European marketing authorization. Within the Commission, the Directorate General (DG) for Enterprise and Industry has the lead on both pharmaceutical legislation and the issues affecting the competitiveness of that sector. The centralized procedure gives the advantage of immediately providing a manufacturer with authorization valid in the entire European Union and European Economic Area. However,

the centralized procedure also requires for the manufacturer to use the same trademark for the product in the entire European Economic Area, and its fees are significantly higher than for other options.

For pharmaceuticals where the use of the centralized procedure is non-mandatory, companies also have the option of the decentralized procedure (Directive 2004/27). In the decentralized procedure, a company chooses a Reference Member State to lead the procedure, and informs that Member State of all of the other Member States (called Concerned Member States) where it would like a marketing authorization. The company sends identical dossiers to the Reference and Concerned Member States. After assessing the dossier, the Reference Member State communicates its assessment to the others, who can accept it and grant marketing authorization. However, if they disagree with the assessment, the procedure enters a dispute-resolution phase, which risks delaying the granting of marketing authorization. Companies can of course seek only a single national authorization if they plan to market their product to one Member State only, though if they plan to seek approval from multiple Member States, they run the risk of delays from disagreements among the states. Once authorization has been granted, Member States do retain the right to restrict the availability within their borders of certain authorized drugs (such as contraceptives) on moral grounds.

All applicants for marketing authorization must prove that clinical studies were conducted ethically and respected the dignity of individuals, regardless of whether or not the studies were conducted in the EU. The specific guidelines for clinical studies are set out in the annex to Directive 2003/63/EC. Unfortunately, Member States' implementation of the guidelines is far from perfect. In certain cases that it needs to justify, a Member State may require additional studies for its national market only. Furthermore, if the pharmaceutical contains genetically modified organisms (GMOs), an environmental impact assessment must be done to determine how the drug will interact with the environment.

Commission regulations provide strict time limits for the acceptance or rejection of a marketing authorization application. Under both the centralized and decentralized procedures, the EMEA or Member State authorities must make a decision within 210 days. Once authorization is granted, it is valid for five years. After this period, the EMEA or competent Member State authority can extend the authorization for an unlimited time period. Health agencies also have the option to grant a renewal for another five years if there is a justified need for pharmacovigilance. If a company does not exercise its marketing authorization within three years, it loses it.

Once a marketing authorization has been granted, companies must obtain a manufacturing authorization if they want to manufacture within the EU or to import to the EU. The time limit for the decision on this application is 90 days. Manufacturing authorization verifies that companies follow the EU's manufacturing standard—called Good Manufacturing Practices (GMPs), meet ethical standards, and do an environmental impact report in the case of bio-pharmaceuticals. GMPs are listed on the European Commission Enterprise website.

All pharmaceuticals must have labels and package leaflets. The packaging must include: information on its name, strength, and form; a statement of active substances per dosage; the method and route of administration; a warning to keep the product out of the reach of children; any other applicable warnings; the expiration date; any special storage requirements; guidance on disposal; the batch number; the authorization number; contact

information for the marketing authorization holder; and the product's name in brail. All of the above information must be written in the official language(s) of the country where the product is sold. Member States are not allowed to prevent pharmaceuticals that follow these requirements from going on the market.

The current European policy on data protection provides for a period of "8+2+1" years: generics manufacturers can apply for a marketing authorization of a given drug eight years after the original product was granted marketing authorization, but the generic product in question could be placed on the market only two years later. In the event that new therapeutic benefits are discovered within the first eight years and the rights holder obtains a new authorization for a new therapy, the data protection can be extended by one year. Also, a new Paediatric Regulation (No 1901/2006) allows for a six-month patent extension for pediatric medicines that complete certain requirements during their marketing authorization procedure, such as the submission of the results of studies.

Advertising of and providing information about prescription pharmaceuticals is severely limited. Television, radio, and print advertising directly to the consumer are prohibited. Limited information, provided it is of an objective and informative nature, can be directed to healthcare providers and doctors. Companies are also not allowed to post product information on the Internet for patients to read. Limited samples are available to doctors to give freely to patients, but cannot be given by industry directly to patients. However, the European Commission recognizes that different EU Member States practice vastly different standards in openness of information. For this reason, the Commission has carried out a consultation and will propose new legislation on information to patients before the end of 2008.

Before the end of 2008, the European Commission also plans to release a legislative package of proposals not only on information to patients, but also on pharmacovigilance and counterfeiting; already several consultations on the subjects have been completed (counterfeiting, pharmacovigilance). Information to patients proposals will aim to harmonize implementation among EU member countries, pharmacovigilance proposals can be expected to streamline existing procedures, and anti-counterfeiting proposals will look to increase regulation and tighten inspections.

Pricing

The Drug Pricing Transparency Directive (89/105/EEC) establishes the basic timelines and guidelines for Member State authorities regarding pharmaceutical pricing and their inclusion in national health insurance systems. The directive requires that national authorities adopt transparent, objective, and verifiable criteria when deciding on price or profit regulations, or the setting up of negative and positive lists for drugs. In general, national authorities must notify drug marketers/producers within 90 days (with a possible 90-day extension for additional information) of the application receipt, for a maximum turn-around time of 180 days. In periods of unusually heavy workload, national authorities can take an extra 60 days to announce a decision. This procedure holds for both price decisions or for inclusion in national health insurance systems.

The transparency directive has led to several court cases in the past decade. The European Court of Justice (ECJ) has brought cases against Finland and Austria; in addition, two drug companies took Belgium to court. In C-424/99, the ECJ ruled that Austria failed to follow the time limits under the Transparency Directive for making decisions. Case C-229/00 determined that Finland was in breach of the transparency requirements for its decisions to establish categorical rankings of products, with different rates of health insurance coverage, ranging from 50% to 100%. Merck and GlaxoSmithKline each won cases against Belgium (C-245/03 and C-246/03); the time periods for reaching a decision on what price the national health system would pay had been exceeded by Belgian authorities. These rulings have affirmed drug manufacturers' access to efficient and transparent decisions regarding the coverage of their product and the right to explanation and appeal if their product is not approved.

However, the courts are not an effective means to ensure compliance by Member States; indeed, only a fraction of such cases are brought by the Commission before the European Court of Justice, so many abuses continue to exist. For example, the Belgian government pressures its doctors to favor generics over patented drugs, while simultaneously allowing legislation to go into effect in 2005 which enacted mandatory price decreases for patented and generic drugs. Similarly, numerous companies report a severe lack of transparency in the setting of Danish reimbursement standards. Finally, France's High Health Authority has confirmed that France will evaluate innovative drugs itself, even if they have already gained approval through the centralized procedure. For more examples of trade barriers see the U.S. Trade Representative's National Trade Estimate Report.

EU Enlargement Led to Exemptions

In 2004, ten new members acceded to the EU. Of those, Cyprus, Poland, Malta, Slovenia, and Lithuania were granted a transitional exemption period to comply fully with pharmaceutical regulations for marketing authorizations and IPR patent protection. Some pharmaceuticals were not under patent in these states due to shorter IPR protection periods, yet were protected in the other EU Member States. These generics could still be produced in the five countries, but the parallel import of non-patent drugs from the five exempted countries was banned in order to protect the IPR of the copyright holders in the other 20 Member States.

For Estonia, Latvia, Hungary, the Czech Republic, and Slovakia, EU regulations were to come into effect upon accession to the EU. Existing marketing authorizations in these countries had to be upgraded to EU standards, and pharmaceuticals that weren't upgraded had to be withdrawn from the market.

In 2007 the Commission concluded a two-year technical consultation with new and applying Member States and decided not to extend previously granted transitional exemptions. Therefore, early in 2008 it requested all Member States—including all recent entries—to immediately implement Directive 2004/27/EC regulating human medicinal products. Nonetheless, as of February 2008, Poland, Malta, Lithuania, and Hungary had still not implemented the articles concerning data protection. The Commission is seeking to bring them into compliance.

Parallel Trade

In the EU, pharmaceutical prices are not subject to free market forces, and manufacturers are unable to act on the basis of supply and demand. Currently, many EU countries ban the sale of a pharmaceutical until the government fixes a price, and since pharmaceuticals are often either purchased or reimbursed by governments, pricing remains a major issue. The resulting price differences among Member States have allowed for parallel trade, in which medicinal products are placed into circulation in one market and then imported into a second market at a markup, without the permission of the local owner of the intellectual property rights. While parallel trade allows European governments and consumers to cut costs, it distorts competition and reduces incentives for innovation. Moreover, patients do not receive improved treatment because of parallel trade; the distributors are the main beneficiaries. While parallel trade is legal, some industry members have established a possible link between parallel trade and counterfeiting, with counterfeits being allowed an entry point through parallel trade.

Competitiveness

The European Commission has been promoting the competitiveness of the pharmaceutical industry in Europe for several years. In 2002, a "High Level Group on Innovation and the Provision of Medicines," called G10, issued recommendations seeking to address the industry's decreasing competitiveness by balancing the provision of sufficient intellectual property protection and the rewarding of innovation with a strong market of generic medicines. Moreover, several G10 recommendations were reflected in Regulation 726/2004 and Directive 2004/27/EC's coverage of patent protection, expedited approval for marketing authorization, and increased speed to markets. Still, Member States continue to exercise their authority to set prices, which often results in sub-market-value prices and parallel trade. The Commission recognizes that price controls and parallel trade reduce incentives for researchers and harm European innovation. Therefore, in 2008 it intends to publish a series of policy options on research competitiveness. While the Commission admits that progress has been slow and the Member States remain hesitant to give up prerogatives, the Commission continues to affirm its dedication to increasing European competitiveness as it pushes to simplify and streamline EU pharmaceutical regulations, increase transparency, and reduce the bureaucratic burden. Furthermore, health research was recently allotted €6.1 billion for research as part of the Seventh Framework Program of 2007. Indeed, European demographic trends—which will see two working age citizens per one retired citizen by 2050—require multiple solutions to the health care difficulties faced by government, industry, and consumers.

For Country Specific Information

As mentioned in the introduction and despite these new regulations emanating from the European Commission, many decisions about pharmaceuticals remain under the purview of Member States and are thus beyond the scope of this market profile. The below websites,

prepared by the U.S. and Foreign Commercial Service, have profiles on the markets and policies of individual European countries.

European export assistance gateway
Showcase Europe: http://www.buyusa.gov/europe/

Country-specific pharmaceutical market overviews
Austria: http://www.buyusainfo.net/docs/x_699408.pdf
Belgium: http://www.buyusainfo.net/docs/x_5976280.pdf
Finland: http://www.buyusainfo.net/docs/x_1640692.pdf
Germany: http://www.buyusainfo.net/docs/x_3931631.pdf
The Netherlands: http://www.buyusainfo.net/docs/x_6115685.pdf
Sweden: http://www.buyusainfo.net/docs/x_3003529.pdf

For More EU-level Information

Regulation EC 726/2004 [centralized procedure]
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf

Directive 2001/83/EC [medicinal products for human use],
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2001_83/dir_2001_83_en.pdf

Directive 2004/27/EC [decentralized procedure],
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2004_27/dir_2004_27_en.pdf

Directive 2003/63/EC's annex (starting on page 4) containing application forms, manufacturing requirements, drug type lists, etc
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2003_63/dir_2003_63_en.pdf

7th EU framework website and calls for proposals listing, www.cordis.europa.eu/fp7/

List of EMEA Nominating Authorities,
http://www.emea.europa.eu/pdfs/aboutus/ExpertsCo.pdf

Summary of European legislation regarding medicinal products,
http://europa.eu/scadplus/leg/en/lvb/l21230.htm

List of fees relating to centralized procedure,
http://www.emea.europa.eu/htms/human/presub/13575708en.pdf

National Trade Estimate Report
http://www.ustr.gov/assets/Document_Library/Reports_Publications/2007/2007_NTE_Report/asset_upload_file170_10944.pdf

EU Pharma Competitiveness page

http://ec.europa.eu/enterprise/phabiocom/index_en.htm

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