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Drug Safety Regulations

European Union

This report concerns the regulation of medicinal products in the European Union.

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EUROPEAN UNION

DRUG SAFETY REGULATIONS

Executive Summary

Drugs, or medicinal products, as they are referred to in the European Union terminology, are strictly regulated to ensure their safety, quality and efficacy. Under EU legislation, there are two procedures available for a marketing authorization within the EU: a) a centralized procedure, which is obligatory for certain medicines and optional for others, and b) a decentralized procedure before the national authorities of a member state. The European Medicines Agency is primarily responsible for granting authorization under the centralized procedure and is required to evaluate, supervise and monitor the safety of medicinal products.

I. Introduction

Under the European Union terminology, the term “medicinal products” or simply “medicines” is used in lieu of “drugs,” which is commonly used in the United States. “Medicinal product” is defined as “any substance or combination of substances presented as having properties for treating or preventing disease in human beings.”¹

The European Union’s legal authority to introduce legislative measures in the field of medicinal products is derived from article 152 of the Treaty on European Union, as amended. In general, the Community is obliged to ensure both “a high level of human health protection” and the smooth operation of a single EU-wide market for pharmaceuticals.² While the organization and delivery of health services and provision of medical care, or setting the prices of medicines remain within the purview of the member states, the EU, in line with national policies, is required to take action to improve public health and prevent human diseases to the extent possible.

¹The definition continues“ ...Or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.” The definition was amended and broadened to take into account the emergence of new therapies, such as gene therapy, radiopharmaceuticals and medicinal products for topical use. See Article 1, of Directive 2004/27/EC Official Journal of the European Communities 2004 OJ L 136 34. This Directive amended Directive 2001/83/EC on the Community Code Relating to Medicinal Products for Human Use 2001 OJ L 311 67.

² Consolidated version of the Treaty on European Union and the Treaty Establishing the European Community. Official Journal of the European Communities 2002 OJ C325, available at <http://eur-lex.europa.eu/en/treaties/index.htm>

At the EU level, medicinal products are strictly regulated to ensure and guarantee three essential elements: quality, safety and efficacy. No medicine can be marketed within the EU territory unless it has been granted a marketing authorization, either by competent national authorities or by the European Medicines Agency (hereafter the Agency). Each has a separate authorization procedure. Under both procedures, the authorization process must be completed within 210 days. The Agency, located in London, is in charge of granting a marketing authorization, under the centralized procedure, which is obligatory for certain medicines.³

II. Current Legislation on Medicinal Products

The legal framework concerning the authorization and market surveillance of medicinal products for human use is embodied in two basic documents:

- Regulation (EC) No. 726/2004⁴ Laying down Community Procedures for the Authorization and Supervision of Medicinal Products for human and veterinary use and Establishing a European Medicines Agency, as amended. The regulation establishes procedures for the authorization, supervision and pharmacovigilance of medicines and provides the legal basis for the European Medicines Agency; and,
- Directive 2001/83/EC on the Community Code Relating to Medicinal Products for Human Use, as amended.⁵

III. European Medicines Agency

The European Medicines Agency is a decentralized body of the European Union. It is established as a legal person and enjoys a broad legal capacity among the member states. Its main responsibility, as described in its official website, is the “protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use.”⁶ The Agency is assisted in its functions by five scientific committees, composed of representatives of EU members and the EEA-EFTA countries (Iceland, Lichtenstein, and Norway), that is, the Committee for Medicinal Products for Human use (CHMP), the Committee for Medicinal Veterinary Use (CVMP), the Committee for Orphan Medicinal Products (COMP), the Committee on Herbal Medicinal Products and the Paediatric Committee (PDCD).⁷ It draws its revenues from contributions from the European Commission and fees paid by the companies in applying for authorizations.⁸ Its management board is composed of one representative of each member state, two representatives of the Commission

³ European Medicines Agency, available at <http://www.emea.europa.eu/>

⁴ *Id.*

⁵ *Id.*

⁶ European Medicines Agency, Structure, Overview, available <http://www.emea.europa.eu/htms/aboutus/emeaoverview.htm>

⁷ Article 56 of Regulation, 726/2004.

⁸ *Id.*, Article 7

and two representatives of the European Parliament.⁹ The Agency is legally represented by its executive director who is appointed by the management board, based on a proposal from the Commission for a period of five years.¹⁰

The Agency has the legal authority to perform the following tasks:

- a) coordinate the scientific evaluation of the quality, safety and efficacy of medicinal products which are subject to community marketing authorization process;
- b) making available to the public any reports or summaries of product characteristics;
- c) disseminate information on adverse reactions through its database;
- d) verifying compliance with the principles of good manufacturing and laboratory practice;
- e) compiling scientific information regarding pathogenic agents which could be used in biological warfare;
- f) cooperating with the World Health organization in evaluating certain medicines; and,
- g) identify any conflict among its opinions issued.

Since July 2007,¹¹ the Agency has been given greater authority regarding the initiation of infringement proceedings before the European Commission. Currently, the Agency may initiate infringement procedure on its own initiative, at the Commission's request, or from a Member State.¹² In such a case, the Agency has to inform the Commission, and may begin the infringement process only upon informing the Member States.¹³ The Agency also enjoys broad powers on requesting additional information and documents. In general, it is required to conclude its investigation and prepare a report within 18 months upon notifying the marketing authorization holder, Commission and Member States.¹⁴ At this point, the Agency has the right to request of the Commission application of financial penalties.¹⁵

⁹ *Id.*, Article 65

¹⁰ *Id.*, Article 64

¹¹ Previously, the Agency had the right to request that the European Commission impose financial penalties to the holders of marketing authorization granted under the centralized procedure, if they violated their obligations arising from Regulation 726/2004.

¹² Regulation No 658/2007 Concerning financial penalties for infringement of certain obligations in connection with marketing authorizations granted under Regulation (EC) No 726/2004, 2007 OJ L 155 10.

¹³ *Id.*

¹⁴ Article 10 of Regulation 658/2007.

¹⁵ *Id.*

IV. Procedures for Marketing Authorization

Based on the above legislation, an applicant, who must be established within the European Union, has the choice of applying for a marketing authorization of a medicinal product through one of the following two procedures:

- a) Centralized procedure as embodied in Regulation 726/2004; or,
- b) National authorization procedures.

Centralized Procedure

The centralized procedure is compulsory for medicines included in the Annex of the Regulation,¹⁶ which include:

- a) Medicines derived from biotechnology;
- b) “Orphan” medicines, that is, medicines used to treat rare diseases;
- c) Medicines which contain a new active substance for the treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorder or diabetes; and,
- d) As of May 2008, medicines which contain a new active substance for the treatment of auto-immune diseases and other dysfunctions of the immune system and viral diseases.

The centralized procedure is optional for the following medicines:

- a) Those containing a new active substance;
- b) Medicines which are deemed a therapeutic, scientific or technical innovation or have a Community dimension; and,
- c) Generic medicines, under certain conditions.¹⁷

National Authorization Procedure

Under the national authorization procedures, the EU members grant authorizations for those medicines that fall outside the scope of mandatory application for the centralized procedures. Applicants have two options:

¹⁶ *Id.*, Article 3, paragraph 1

¹⁷ Article 3, paragraph 2 and 3 of Regulation 726/2004.

- a) the decentralized procedure, under which application can be made for simultaneous authorization in more than one EU member states; and,
- b) mutual recognition procedure, where a medicine is first authorized in one EU member state and then recognition is sought of the validity of the original marketing authorization in another member state.¹⁸

The Committee for Proprietary Medicinal Products is charged with reviewing any issues concerning the granting, variation, suspension or withdrawal of marketing authorization.¹⁹ If two or more EU Members disagree on issues related to authorization of medicines either under the decentralized or the mutual recognition procedure, the Co-ordination Group for Mutual Recognition and Decentralized Procedures–Human (CMD(h)) is to deal with and resolve these issues.²⁰ The CMD(h) is composed of one representative of each member state, and the EEA-EFTA states (Iceland, Liechtenstein and Norway), for a renewable period of three years.

Once a marketing authorization is granted, the medicinal product is classified as either subject to prescription or not subject to prescription by the competent national authorities.²¹ The marketing authorization is valid for five years, and can be renewed once . Afterwards, it is of unlimited validity.

Authorization and Supervision of Medicines

Under the centralized and decentralized procedure, an applicant must include in the application the particulars and documents specified in Articles 8(3), 10, 10a, 10b or 11 and Annex 1 of Directive 2001/83/EC, along with a statement indicating that the clinical trials done outside the European Union meet the ethical requirements of the above stated Directive.

Applicants must gather the particulars and the documents that must be filed, together with an application for marketing authorization and must present them in four parts:

- 1) Summary of the Dossier containing data related to the medicinal product, a summary of its characteristics, and expert reports;
- 2) information regarding the chemical, pharmaceutical and biological testing of medicinal products;
- 3) toxicological and pharmacological tests; and,

¹⁸ <http://www.hma.eu/cmdh.html>

¹⁹ Article 27 of Directive 2001/83/EC.

²⁰ It was established by Article 27 Directive 2004/27/EC on the examination of any question relating to marketing authorization of a medicinal product in two or more Member States in accordance with the mutual recognition procedure.

²¹ Art. 24, paragraph 3, of Directive 2004/27/EC amending Directive 2001/83/EC on the Community Code Relating to Medicinal Products for Human use, OJ L 136/34

- 4) clinical documentation.²²

In addition, applicants are required to follow a number of guidances and to also take into account the Community guidelines concerning the quality, safety and efficacy of medicinal products, published by the European Commission in the Rules Governing Medicinal Products in the European Community.²³

The authorization process within the Agency includes the following steps:

- a) The applicant submits the application for authorization along with a fee to the Agency. The Committee for Medicinal Products for Human Use (CMPH), established in 2004, is part of the Agency and is exclusively responsible for issuing the Agency's opinions on all issues related to medicinal products for human use.²⁴
- b) The Agency is required to ensure that (CMPH) to give its opinion within 210 days upon receipt of a valid application.
- c) The CMPH is responsible for verifying the particulars and documents within a period of at least 80 days. The period can be extended.
- d) The applicant can be requested to supplement the documents provided or to undergo an inspection of the manufacturing site of the medicine.

The Agency must inform the applicant if the CMPH issued an opinion to the effect that:

- the application fails to meet the criteria for authorization;
- The summary of the characteristics of the medicine proposed need to be amended;
- The labeling or package leaflet of the medicine does not meet the requirements of Title V of Directive 2001/83/EC; and/or
- The authorization is granted subject to certain conditions, as contained in Articles 14(7) and (8).

The applicant may, within 15 days of receipt of such opinion, request that the CMPH reevaluate its opinion, based on detailed grounds that need to be submitted within 60 days after

²² See Annex I of Directive 2001/83/EC on the Community Code Relating to Medicinal Products for Human Use 2001 OJ L 311 67.

²³ Commission Rules Governing Medicinal Products in the European Community, Volume II, Notice to Applicants for Marketing Authorization for Medicinal Products for Human Use in the Member States of the European Community and Volume III and its supplements: Guidelines on the Quality, safety and Efficacy of Medicinal Products for Human Use, available at http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/eudralex_en.htm

²⁴ Article 5 of Regulation 726/2004, 2004 OJ L 136 1.

receipt of the opinion. The CMPH, within 60 days upon receiving the request for reevaluation, will reexamine its initial opinion. Following the adoption of the CMPH's final opinion, the Agency will forward a copy of it to the Commission, the member states and the applicant along with a report that contains a detail assessment of the file, including the conclusions that must be well substantiated.²⁵

If the opinion recommends an authorization, the following documents will be attached to the opinion:

- a) details of any conditions or restrictions imposed on the supply or use of the medicine, including conditions under which the medicine will be made accessible to patients;
- b) restrictions or conditions pertaining to the safe and effective use of the medicine;
- c) a draft text of the labeling and package leaflets, as proposed by the applicant;
- d) d) a draft summary of the characteristics of the product; and,
- e) the assessment report.

V. Pharmacovigilance

The term “pharmacovigilance” refers to the monitoring of the safety and quality of medicines, after authorization is granted and the medicines are placed in the market. This task is shared by the Agency and the national competent authorities. Based on the data supplied by the national authorities, the Committee for medicinal Products for Human Use may draft recommendations to amend the marketing authorizations. EU members are required to establish a pharmacovigilance system in order to collect information for effectively surveying medicinal products, especially adverse effects.²⁶ Members are also required to encourage health care professionals to report suspected adverse effects to the competent national authorities. When such reporting is part of the conditions of marketing authorizations, then the members must ensure that doctors and other involved in the health sector report suspected serious or unexpected adverse reactions.²⁷

In addition, holders of a marketing authorization are also responsible for ensuring continued control and supervision of safety and efficacy of medicines. They are required, *inter alia*, to appoint a qualified person to be exclusively responsible for pharmacovigilance; to maintain detailed records of all suspected adverse effects of the medicine in question, either within EU or in a third country;²⁸ and, to notify the competent authority of all suspected serious

²⁵ *Id.*, Article 5.

²⁶ Article 102 of Directive 2001/83/EC

²⁷ Article 101 of the Directive, see also Articles 21-29 of Regulation 726/2004

²⁸ Article 104 of the Directive, *supra* note 22.

side-effects communicated by health care professionals within 15 days upon receipt of information.

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