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COMPASSIONATE USE IN EUROPE: A PATCHY FRAMEWORK FOR EARLY MARKET ENTRY

It has become a paradigm in most jurisdictions that market entry of pharmaceuticals requires marketing authorization. However, for ethical reasons, an exemption is made in some jurisdictions for compassionate use. This *Commentary* provides an overview of the regulation of compassionate use in Europe, taking into account, *inter alia*, the recently issued regulation of the German Ministry of Health.

THE EUROPEAN REGULATION

Under the Community Code for Medicinal Products for Human Use (originally Directive 65/65/EEC, now Directive 2001/83, the "Community Code"), pharmaceuticals—with very few exceptions—require marketing authorization for placing on the market. It should be recalled that the introduction of this requirement is basically the raison d'être of the European legislation, which was conceived to exert prior medical-scientific control over products that might create health risks for patients.

However, this preventive measure poses an ethical dilemma in specific cases where a product under development has proven efficacy but has not yet obtained marketing authorization. If there is no alternative treatment available, patients might be deprived of potentially lifesaving or life-prolonging medication. The compromise is "compassionate use," which exempts distribution of the product from the marketing-authorization requirement under defined circumstances.

Compassionate use needs to be distinguished from "off-label use"—the latter is the use of an authorized product outside its authorized indication(s), whereas the former is the use of a product that has not (yet) been authorized at all. Compassionate use also differs from the use on a named-patient basis of a product lacking marketing authorization because it addresses an entire group of patients. Last but not least, compassionate use differs from the individual importation of products authorized abroad but not in the country of importation because, once again, it is

designed to meet the needs of a group of patients rather than those of an individual, and it does not require foreign marketing authorization.

Compassionate use has been known for some time on the national level—France introduced its legislation in 1994. However, on the European level, it was not until 2004 that the European regulation on centrally authorized pharmaceuticals (Regulation 726/2004/EC, or the "European Regulation") provided an explicit exemption from the marketing-authorization requirement for products eligible for central marketing authorization in cases of compassionate use. It is of note that the European Regulation allowed the Member States to decide individually whether to allow compassionate use—a situation that has resulted in a patchwork of national regulations. One of the oddities of the European framework is the absence of an exemption in the Community Code for products that can be authorized only on a national basis. This, however, has not prevented Member States from including products in compassionate-use legislation that are headed for national authorization.

No data on compassionate use on the European level is currently available. However, data released by the French Health Products Safety Agency (*Agence française de sécurité sanitaire des produits de santé*, or "AFSSAPS") indicate that by 2007, more than 20,000 patients had been treated with over 200 products under the French legislation for compassionate use. This indicates the relevance of compassionate use for the ethical treatment of patients.

Nonetheless, compassionate use is subject to a range of conditions under the European Regulation. The drug in question must either be undergoing clinical trials or be the subject of an application for (central) marketing authorization. Compassionate use is allowed only for patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily with authorized products. The Committee for Medicinal Products for Human Use (the "CHMP") of the European Medicines Agency ("EMA") has issued a guideline (EMEA/27170/2006, the "CHMP Guideline") which specifies that the absence of an authorized treatment alternative applies to the specific Member State in which compassionate use is envisaged. The fact that an authorized product is available for therapy in another Member State therefore does not preclude compassionate use. Compassionate use shall be available for a group of patients, that is, a predetermined set of patients. Compassionate use does not prejudice therapy on a named-patient basis.

If a compassionate-use program has been set up, product supply has to be guaranteed for the period between the issuance of marketing authorization and the first (commercial) placing on the market. The European Regulation is silent on whether or not the patient may be charged for the product.

The Member States are free to devise their own national procedures for compassionate use. However, they are required to notify EMA of any allowed compassionate use and may request the opinion of the CHMP on specific compassionate-use programs. The CHMP may set out conditions for the use and supply of the product as well as patient eligibility; its first two opinions were issued early this year on the compassionate use of avian flu vaccines by Roche and GlaxoSmithKline.

Compassionate use may not be employed by generic manufacturers for early entry, where the patent of the originator has not yet expired, as it is not privileged under the European framework for research exemptions, equivalent to the Hatch-Waxman exemption. For the same reason, originators require freedom to operate if they want to set up compassionate-use programs.

One of the major shortcomings of the European legislation is the lack of specific provisions governing the information on existing compassionate-use programs that may be made available to patients. European legislation does not allow the advertising of products that have not yet obtained marketing authorization. And while companies may claim that information on compassionate-use programs does not qualify as advertising, the concept of advertising is very broad under European law. The current heated political debate on proposed legislation allowing the provision of information to patients for prescription-only drugs demonstrates that advertisements and information are separated by a very thin line, if at all.

FRANCE

Legislation on premarket approval for compassionate use (*autorisation temporaire d'utilisation de cohorte*, or "*ATU de cohorte*") was introduced in France in 1994 by the Bioethics Act and amended by the second Bioethics Act in 2004. The legislation covers drugs that are undergoing clinical trials or have already passed them. In order to apply for an *ATU de cohorte*, a company must file an application for marketing authorization for the drug or must undertake to submit such application before a specific deadline.

The applicant for an *ATU de cohorte* shall establish the seriousness or rarity of the condition the drug is meant to cure as well as the absence of appropriate existing treatment. (In a decision from 2005, the French Supreme Administrative Court (*Conseil d'Etat*) ruled that a drug which is substitutable for the drug object of the *ATU de cohorte* but not immediately available cannot be considered an appropriate existing treatment and should therefore not preclude the granting of an *ATU de cohorte*.)

The application for an *ATU de cohorte* must be filed with AFSSAPS. The legislation provides that the application file shall be composed of the elements and information necessary for an application for marketing authorization. The final decision will be issued after the opinion of the Commission for Marketing Authorization has been rendered to AFSSAPS, but the legislation does not provide a specific time frame for the issuance of the opinion.

The *ATU de cohorte* is granted for a term of one year. The granting of the *ATU de cohorte* automatically leads to the approval of the protocol for the therapeutic use of the drug at stake. This protocol shall be communicated to the doctors who are likely to prescribe the drug, the pharmacists who are likely to dispense it, the regional centers of drug monitoring, and the poison-control centers. The applicant must systematically provide the following to AFSSAPS, the doctors, the pharmacists, the regional drug-monitoring centers, and the poison-control centers:

- Information relating, notably, to the drug's real conditions of use and the characteristics of the population benefiting from the drug; and

- A synthesis of all data gathered on the drug's real conditions of use and the efficiency of the product.

The *ATU de cohorte* can be renewed following the examination of a new application pointing out all new data obtained during the first period of use of the drug and specifying the quantities of drugs delivered during that time, as well as information from the drug-monitoring reports. When the conditions for the granting of an *ATU de cohorte* no longer exist or if public-health concerns so require, the *ATU de cohorte* may be suspended or withdrawn by a motivated decision that must specify the means of recourse against the decision. The *ATU de cohorte* expires as soon as the drug in question receives marketing authorization.

GERMANY

Legislation on compassionate use was introduced in Germany in 2005 by an amendment to the German Drug Act in the wake of the amendment to the European Regulation. The legislation initially covered only products eligible for central marketing authorization and was subsequently expanded to cover products headed for national authorization. In 2009, the legislation was further amended to impose the requirement that products must be supplied free of charge. This is considered a serious disincentive to setting up compassionate-use programs, particularly for start-up biotechnology companies that develop pharmaceuticals with high costs of goods, like antibodies.

Following a five-year delay, the German Ministry of Health now has issued a regulation covering the administrative procedure for compassionate-use programs (*Verordnung über das Inverkehrbringen von Arzneimitteln ohne Genehmigung oder ohne Zulassung in Härtefällen*). This regulation entered into force on July 22, 2010, and is applicable (only) to compassionate-use programs for products that have not yet obtained marketing authorization anywhere in the

EEC. It is unclear why products that are lacking marketing authorization in Germany but have received national authorization elsewhere in the EEC are not covered by the regulation. Perhaps this is a drafting error, which may be amended in the future. The regulation requires the competent federal authority, in most cases Germany's Federal Institute for Drugs and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte*) to be notified of the proposed compassionate-use program. The authority may object to the program. In the absence of an objection, the program may be launched as of receipt of the acknowledgment of receipt of the notification by the authority. The authority shall provide such acknowledgment within two weeks or, in the case of genetically modified organisms, within "a reasonable time." This procedure effectively amounts to an approval process.

The notification requirements are comprehensive. *Inter alia*, the person who is to be responsible for the compassionate-use program must be appointed and notified. Among other substantive information, the criteria for the patient group and an estimate of its size must be submitted. The notification must include the reasons why treatment alternatives are lacking; data on the quality and efficacy of the product; and a draft summary of product characteristics or, in the alternative, the investigators' brochure used for the clinical trials. A copy of the product information intended for the patient (equivalent to the package information leaflet) must be provided, along with a description of how the treating physician shall obtain informed patient consent (equivalent to the informed patient consent required for participation in clinical trials). The regulation also specifies notification requirements on pharmacovigilance data and sets out labeling requirements for products used in the program.

Unless a compassionate-use program expires due to the issuance of marketing authorization, it ends one year after receipt of the acknowledgment of receipt issued by the competent federal authority. An additional application may be filed, resulting in the extension of the program.

There exist serious legal doubts as to the validity of the regulation, which hopefully can be addressed in the near future by amendments to the German Drug Act, some of which have already been introduced into the legislative process. However, such amendments might result in amendments of the new regulation as well. Therefore, manufacturers should keep an eye on current legislative developments in Germany.

ITALY

Italy has not yet implemented legislation on compassionate use. However, Legislative Decree No. 219 from 2006 requires the Italian Ministry of Health to adopt a ministerial decree to establish the criteria and procedures for using medicines not yet authorized in Italy, including those for compassionate use, in light of the CHMP Guideline.

In the meantime, the following alternatives are available, other than using products in clinical trials:

- In accordance with Law No. 648/1996, it is possible to import and use a medicinal product not (yet) authorized in Italy but already marketed in other Member States in cases where there are no therapeutic alternatives, provided the use of such product has obtained the prior approval of the Commission of the Italian Agency for Pharmaceuticals (*Agenzia Italiana del Farmaco*); and

- In accordance with Law No. 94/1998, it is possible to use a medicinal product in a different indication (an "off-label use") under certain specific conditions.

SPAIN

The use of pharmaceuticals that have not (yet) been authorized by the Spanish Pharmaceuticals Agency (*Agencia Española de Medicamentos y Productos Sanitario*s, or the "AEMPS") is regulated by Law 29/2006, which deals with guarantees and the rational use of pharmaceuticals and sanitary products. Law 29/2006 guarantees the availability of pharmaceuticals in specific situations and with special authorization: patients not included in clinical trials may be prescribed certain products as part of the goal to meet the special-treatment needs of certain patients.

In 2009, the Spanish government passed Royal Decree 1015/2009, regulating the availability of pharmaceuticals in special situations, including compassionate use. This decree requires the meticulous application of Law 41/2002, which in turn regulates the autonomy of patients. Law 41/2002 specifies the rights and obligations related to the provision of information and clinical documentation to patients, including a patient's right to choose among the available clinical options once he or she is in possession of all relevant information. This law also provides the conditions for obtaining the patient's consent to treatment.

Royal Decree 1015/2009 further allows for compassionate use of pharmaceuticals that are under clinical investigation among patients who are not involved in clinical trials.

Compassionate use is permitted under the following conditions:

- The patient must have a chronically or seriously debilitating disease or one that is considered to be life-threatening, and which cannot be treated satisfactorily with authorized products;

- The product must be (1) subject to an application for marketing authorization, or (2) undergoing clinical trials.

- The sponsor of the clinical trials or the applicant for marketing authorization must have consented to supply the product for compassionate use.

Compassionate use may be authorized for an individual or, temporarily, for a group; the latter option simplifies compassionate use by eliminating the need for separate applications for individual access to a product lacking marketing authorization. The AEMPS may allow the temporary use of a product under investigation independently from the clinical trials when the product is in the advanced stages of clinical investigation, resulting in data supporting a marketing authorization, or when marketing authorization has been requested, as long as use of the product by a significant group of patients is foreseen.

Once issued, the temporary authorization shall specify the conditions and requirements under which the product may be used outside the scope of clinical trials without requiring individual authorization for each patient.

Management of the medical center providing the treatment must make sure that each patient to be treated with the product meets the requirements provided in the temporary authorization. Furthermore, the center's management shall: 1) obtain the patient's written informed consent to treatment before supplying the pharmaceutical, and 2) inform the AEMPS of each patient benefiting from the temporary-use authorization.

THE UNITED KINGDOM

There is no legislation in the U.K. that specifically implements a compassionate-use program as allowed under Article 83 of the European Regulation. However, the U.K. makes use of the derogation under Article 5 of the Community Code that allows Member States to put in place national arrangements allowing authorized health-care professionals to commission the manufacture of medicinal products lacking marketing authorization (referred to as "specials") to meet the special needs of individual patients. The framework in place in the U.K. provides largely the same outcome as Article 83 of the European Regulation and in effect is similar to the European compassionate-use program.

There are two pieces of U.K. legislation that provide for the importation and manufacture of specials: the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994 (SI 1994/3144), which set out the conditions whereby specials may be manufactured and supplied, and the Medicines for Human Use (Manufacturing, Wholesale Dealing and Miscellaneous Amendments) Regulations 2005 (SI 2005/2789), which deal with the importation and supply of specials. These regulations are administered by the Medicines and Healthcare products Regulatory Agency ("MHRA"), which has published a guidance note on the manufacture, importation, and supply of specials entitled "The Supply of Unlicensed Relevant Medicinal Products for Individual Patients."

Specials may be manufactured and supplied for individual patients in an exemption from the marketing authorization laws provided under SI 1994/3144. This exemption applies to patients who have special clinical needs that cannot be met by authorized products. To meet these needs, the exemption allows the manufacture and supply of specials under the following conditions:

- There is a bona fide unsolicited order;
- The product is formulated in accordance with the requirement of a U.K.-registered doctor or dentist;
- The product is for use by patients of that doctor or dentist and under his or her direct supervision; and
- The product is distributed by way of wholesale dealing by the holder of a wholesale dealer's license.

If a special is manufactured in the U.K., the manufacturer must hold a manufacturer's (specials) license issued by the MHRA. A special may not be advertised, and if an equivalent product authorized in the U.K. that could meet the patient's needs is available, then the special should not be supplied.

The importer of a special must hold the appropriate wholesale dealer's license (for imports from within the EEA) or a manufacturer's specials license valid for import (for imports from outside the EEA) and must also comply with the following license conditions:

- The importer must notify the MHRA on each occasion that it intends to import a product lacking marketing authorization in the U.K.;
- Importation may proceed only in the absence of notification within 28 days from the MHRA that it objects to the importation. The MHRA will object if it has concerns about the safety or quality of the product, if an equivalent authorized medicinal product is available, or if it is not satisfied that there is a special need for the supply of the special;
- The license holder may not issue an advertisement, catalogue, or price list relating to the medicine. However, the general restriction on selling or offering to sell products that do not have marketing authorization in force does not apply to the sale or offer to sell these specials.

A special may be imported only in accordance with SI 2005/2789. This regulation provides, relevantly, that the license holder may import products without marketing authorization only in response to an order that satisfies the requirements set out in SI 1994/3144: namely, that there is a bona fide unsolicited order, the product is formulated in accordance with the requirement of a U.K.-registered doctor or dentist, etc.

It should be noted, however, that the MHRA is currently reviewing the regulatory arrangements governing the manufacture, importation, and supply of medicines lacking marketing authorization. An interim report was released in May 2009 that highlighted the five main objectives of the reform:

- A clinician should have the ability in appropriate circumstances to exercise his or her professional judgment to commission the supply of a special to meet the special needs of an individual patient;
- Public-health protection should be improved;
- There should be clear responsibility and accountability for protecting the safety and rights of patients;
- Regulatory safeguards should meet the principles of better regulation: proportionality, targeting, consistency, transparency, and accountability; and
- Arrangements should complement and not undermine the wider system for the authorization of medicines.

Therefore, it is possible that the regulations and practices currently in place in the U.K. with respect to medicines lacking marketing authorization may change in the near future.

CONCLUSIONS

If a company sets up a compassionate-use program in Europe, it has to comply with a patchwork of national regulations. The European Regulation provides a framework for products eligible for central marketing authorization and at the same time serves as a point of reference for national legislation on products headed for national authorization. However, national authorities might take divergent views on compassionate-use programs, not least on the unavailability of treatment options. In such a case, the CHMP might have to resolve the issue by delivering an opinion. Such opinions might increasingly be requested now that Germany has enacted national legislation providing the competent federal authorities with control over German compassionate-use programs. Currently, compassionate-use programs in three major European markets (France, Germany, and Spain) are subject to tight supervisory control, while regulations are upcoming in two additional major markets (Italy and the U.K.).

On the upside, compassionate-use programs in accordance with the respective national European legislation not only provide companies with the opportunity to meet ethical obligations towards patients in need, but also offer the possibility of gaining access to patients prior to marketing authorization and of obtaining clinical experience with drugs outside the controlled environment of clinical trials.

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