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Life Sciences Health Industry Alert

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Pharmaceutical Package: Safe, Innovative and Accessible Medicines and A Renewed Vision For the Pharmaceutical Sector

The European Commission published on December 10, 2008 a series of political measures and legislative proposals, the so-called "Pharmaceutical Package."

This series included the "Communication on a renewed vision for the pharmaceutical sector," which reflected on ways to improve market access and develop initiatives to boost European Union (hereinafter referred to as "EU") pharmaceutical research.

With regards to the political measures, the European Commission has offered, inter alia, to:

- Make pricing and reimbursement more transparent, by way of discussion with the Member States.
- Create schemes which aim at developing pharmaceutical research within the European Union.
- Improve the safety of medicines worldwide by accentuating cooperation with the most influential partners (e.g., United States, Japan, Canada).
- Reinforce cooperation with partners that are coming to light (e.g., Russia, India, China).

With respect to the legislative proposals, the European Commission has published three separate sets of proposals amending Directive 2001/83/EC on the Community Code of medicinal products and Regulation 726/2004 on medicinal products obtained through centralized procedures:

1. A proposal amending Directive 2001/83 as "regards information to the general public on medicinal products subject to medical prescription" (Information to patient);
2. A proposal amending Directive 2001/83 and a proposal amending Regulation 726/2004 as "regards pharmacovigilance" (The EU pharmacovigilance system); and,
3. A proposal amending Directive 2001/83 as "regards the prevention of the entry into the legal supply chain of medicinal products which are falsified in relation to their identity, history or source" (Counterfeit Medicines).

I. Information to patients: laying down clear rules on information provided by pharmaceutical companies on prescription-only medicinal products

EU institutions, healthcare stakeholders and EU citizens seem to agree that communication with patients and the general public on health issues and prescription medicines should be improved in order to have better informed patients and to involve them in making decisions regarding their health.

Although advertising of prescription-only medicines to the general public is currently forbidden by Directive 2001/83/EC on "the Community code relating to medicinal products for human use," its Article 86 (2) provides that certain information activities are not exempted:

- "correspondence, possibly accompanied by material of a nonpromotional nature, needed to answer a specific question about a particular medicinal product,
- factual, informative announcements and reference material relating, for example, to pack changes, adverse-reaction warnings as part of general drug precautions, trade catalogues and price lists, provided they include no product claims,
- statements relating to human health or diseases, provided there is no reference, even indirect, to medicinal products".

The proposal "amending Directive 2001/83/CE on the grounds of information to the general public on medicinal products subject to medicinal prescription" [SEC(2008)2667, SEC(2008) 2668] aims at

ensuring that pharmaceutical companies can provide information on their prescription-only medicinal products to the general public, while maintaining the existing advertising ban.

The key elements of the patient information proposal are the following:

1. **Authorization of information on prescription-only medicinal products directly to the public**

   Proposed new Article 100 a) clarifies that the provision of information on prescription-only products by marketing authorization holders is allowed under certain conditions:

   "1. Member States shall allow the marketing authorisation holder to disseminate, either directly or indirectly through a third party, information to the general public or members thereof on authorised medicinal products subject to medical prescription provided that it is in accordance with the provisions of this Title. Such information shall not be considered advertising for the purposes of the application of Title VIII.

   2. This Title shall not cover the following:

   (a) information relating to human health or diseases, provided that there is no reference, even indirect, to medicinal products;

   (b) material provided by the marketing authorisation holder to healthcare professionals for distribution to patients."

2. **Types of authorized information**

   According to new Article 100 b), only some information about prescription-only medicinal product is allowed:

   "(a) the summary of product characteristics, labeling and package leaflet of the medicinal product, as approved by the competent authorities, and the publicly accessible version of the assessment report drawn up by the competent authorities;

   (b) information which does not go beyond the elements of the summary of product characteristics, labeling and the package leaflet of the medicinal product, and the publicly accessible version of the assessment report drawn up by the competent authorities, but presents them in a different way;

   (c) information on the environmental impact of the medicinal product, prices and factual, informative announcements and reference material relating, for example, to pack changes or adverse-reaction warnings;

   (d) medicinal product-related information about non-interventional scientific studies, or accompanying measures to prevention and medical treatment, or information which presents the medicinal product in the context of the condition to be prevented or treated."

3. **Authorized channels of information**

   New Article 100 c) defines these authorized channels in order to exclude unsolicited means of dissemination:

   "Information on authorised medicinal products subject to medical prescription disseminated by the marketing authorisation holder to the general public or members thereof shall not be made available on television or radio. It shall only be made available through the following channels:

   (a) health-related publications as defined by the Member State of publication, to the exclusion of unsolicited material actively distributed to the general public or members thereof

   (b) internet websites on medicinal products, to the exclusion of unsolicited material actively distributed to the general public or members thereof

   (c) written answers to requests for information of a member of the general public."

4. **High quality standard for information disseminated**

   Any information to the general public on prescription-only medicinal products must comply with the set of quality criteria defined by new Article 100 d). The content and presentation of information must be:

- Objective and unbiased
- Take into account the general needs and expectations of patients
- Based on evidence and be verifiable and include a statement on the level of evidence

- Up-to-date and include the date of publication or last revision of the information
- Reliable, factually correct and not misleading
- Understandable for the general public or members thereof
- Clearly state the source of the information indicating the author and giving references to any documentation that the information is based on
- Not contradict the summary of product characteristics, labeling and patient information leaflet of the product, as approved by the competent authorities

The proposal furthermore introduces the obligation for Member States to establish a monitoring system to ensure that the mentioned provisions on content of information, quality standards and dissemination channels comply with and ensure its enforcement in case of non-compliance. Specific monitoring rules for information disseminated through websites must be established to take into account the cross-frontier nature of information provided over the Internet.

This legislative proposal defines clear rules: pharmaceutical companies are authorized to provide information about prescription-only medicinal products, subject of an ex ante control. This authorized information must comply with high-quality standards.

According to European consumers' organizations, it is difficult to make a clear distinction between non-promotional information and advertising. The pharmaceutical industry cannot be considered a reliable source of unbiased information, due to an obvious and unavoidable conflict of interest.

The European Federation of Pharmaceutical Industries and Associations (EFPIA) does not consider Direct-to-Consumer advertising as an appropriate model for Europe. Nevertheless, it seems overriding to improve access for all ED citizens and patients to non-promotional health and medicines information in their language. For this reason, the European Commission proposes to oblige Member States to monitor information that companies provide and sanction companies in the event of non-compliance. A monitoring system with efficient governance and enforcement procedures would be the most practical way forward.

EFPIA considers that this approach would help ensure that information to patients on prevention, diagnosis, treatment and management of diseases meets the highest quality standards and provides the greatest benefits to patients.

II. The ED pharmacovigilance system: improving patient protection by strengthening the EU system for monitoring the safety of medicinal products

Numerous and significant weaknesses have been revealed in current pharmacovigilance, notably: duplicative assessments by national authorities, relatively limited ED coordination, cumbersome oversight of companies' pharmacovigilance mechanisms by the authorities, lack of transparency, etc.

Accordingly, the second legislative proposals aim at simplifying and strengthening the current pharmacovigilance system for both products authorized through the centralized procedure and those authorized nationally.

The main measures proposed are the following:

1. **Role and responsibilities clarified**

   In the contemplated future mechanism, Member States shall remain central to the pharmacovigilance system with, however, an increased cooperation and work-sharing mechanism:

   - Thus, "unless urgent public announcements are required for the protection of public health, the Member States, the Agency and the Commission shall inform each other not less than twenty four hours prior to a public announcement relating to information on pharmacovigilance concerns" (proposed Art. 106a-2 of the Directive).
   - For medicinal products authorized in more than one Member State, the EMEA "shall be responsible for the coordination between national competent authorities of safety announcements and shall provide timetables for the information being made public"(proposed Art. 106a-3 of the Directive)
   - A new scientific committee, the Pharmacovigilance Risk Assessment Advisory Committee, is created within the EMEA. At the request of the EMEA, such Committee shall notably provide advice on the contemplated coordinated safety announcements (new Art. 106a).

- The EMEA shall :
  - monitor "selected medical literature for reports of suspected adverse reactions to medicinal products containing certain active substances" (new Art. 27 of the Regulation)
  - "establish and make public a list of medicinal products for human use under intensive monitoring" (new Art. 23 of the Regulation).

2. Transparency and communication

- The proposed new Article 1.11 of the Directive amends the definition of "adverse reaction" to ensure that "it not only covers noxious and unintended effects derived from the authorised use of a medicinal product at the normal doses but also medications errors and uses outside the authorized summary of the product characteristics, including the misuse and abuse of the product."
- The Eudravigilance database should become the single point of receipt of pharmacovigilance information for medicinal products authorized in the ED.

  The direct and single reporting to the Eudravigilance database will apply both to medicinal products authorized in the Member States and to medicinal products authorized through the centralized procedure.

  According to the proposed new Article 24 of the Regulation:
  - the Eudravigilance database shall include information on adverse reactions arising both from the use of the products within the terms of the marketing authorization and from another use (misuse, abuse, medication errors, those occurring during studies)
  - the Eudravigilance database shall be fully accessible to the national authorities and to the Agency and the Commission
  - the Eudravigilance database shall be accessible to the marketing authorization holders to the extent necessary for the compliance with their pharmacovigilance obligations
  - data held on the Eudravigilance database will be made publicly accessible in an aggregated format together with relevant explanations of interpretation.
  - Each Member State must set up a national safety web portal linked to the European medicine safety web-portal. Through such national safety web portal, the Member States shall make public at least:
    - the risk management systems
    - the list of medicinal products under intensive monitoring pursuant to the proposed new Article 23 of the Regulation
    - the web-based structured forms for reporting suspected adverse reaction by healthcare professionals and patients.
  - The summary of the product characteristics and the package leaflet shall include a new section relating to the "essential information necessary to use the medicine safely and effectively" (new Art. 11(3a) & new Art. 59(l)aa of the Directive).

3. Obligations of the marketing authorization holder

- Current legislation requires a "detailed description of the pharmacovigilance system" to be submitted in marketing authorization applications.

  The proposals simplify the existing requirements by introducing the concept of "pharmacovigilance system master file". Such a file designates the document including a detailed description of the pharmacovigilance system.

  In the proposed procedure, the applicants shall only provide for a "summary of the pharmacovigilance system" and shall mention a reference to the site where the above-mentioned pharmacovigilance system master file is maintained and accessible (new Art. 8(3)ia of the Directive and new Art. 18(3) & 26(5) of the Regulation).
- Marketing holders and the Member States shall record suspected adverse reactions notified by patients and healthcare professionals (new Art. 107 & 107a of the Directive).

4. Risk management planning and non-interventional studies

- Unlike the current applicable system which provides that applicants for a marketing authorization may, if they consider it appropriate, provide a risk management system

for specific products, the proposed new legislations set out an explicit legal basis for competent authorities to subject a marketing authorization to a detailed description of the risk management system for any new products or for existing products due to safety concerns (new Art. 8(3)iaa of the Directive and new Art. 9(4)ca of the Regulation).

- After the granting of a marketing authorization, the national competent authorities (or the EMEA for products authorized through the centralized procedure) may require the marketing holder to conduct post-authorization safety studies (new Art. 22a of the Directive & new Art. l0a of the Regulation).
- New guiding principles for non-interventional post-authorization safety studies are introduced in the new Chapter 4 of the Directive and new Article 28b of the Regulation (e.g. absence of promotional aspect, follow-up of the results to the authorities, possible variations of the marketing authorizations, etc.)

5. **Periodic safety update reports and other safety related assessments**

   Currently, periodic safety update reports are mainly detailed listings of individual cases. As case reports are already recorded in the Eudravigilance database, the second legislative aims at:

   - Reducing the content of the periodic safety update reports that, pursuant to the new Article l07b.1 of the Directive, shall only include:
     - "summaries of data relevant to the benefits and risks of the medicinal product"
     - "a scientific evaluation of the risk-benefit balance of the medicinal product." Such evaluation shall "be based on all available data, including data from clinical trials in unauthorized indications and populations"
     - "all data relating to the volume of sales of the medicinal product and any data in possession of the marketing authorization holder relating to the volume of prescriptions."
   - Removing the routine reporting for low risk, old and well-established products (new Art. 107b.3 of the Directive)
   - Ensuring that the reporting shall be linked to the risk management system for newly authorized products (new Art. l07h of the Directive)
   - Introducing a single submission and a single assessment of periodic safety update reports for medicinal products authorized in different Member States and containing the same active substance (new Art. l07c of the Directive).
   - Ensuring that, as a result of the assessment of the periodic safety update reports, the national authorities shall consider any required action concerning the marketing authorization such as variation, suspension, etc. (new Art. 107f of the Directive).

III. Counterfeit medicine: protecting the legal supply chain against counterfeit medicinal products

Counterfeit medicinal products are an increasing concern for the patients, industry, EU and national legislator. A counterfeit medicinal product was formerly defined as any medicine created without the authorization of the owner of the patent. This denomination nowadays encompasses medicinal products which are illegal and false representations relating to the products' identity, history or source.

This potential harm to public health is the reason why the war declared on it by public authorities is in full swing. In France, many seizures are being processed each year. In Belgium, the biggest seizure in Europe was processed in October 2008 (2,134 millions of medicine pills seized).

Counterfeit medicinal products constitute a major threat to public health and safety, for three main reasons:

- First, their number has greatly increased. Indeed, between 2005 and 2007, the increase of counterfeit medicine at the border of the EU has increased by 380%.
- Secondly, the risk profile has changed. Nowadays, they are increasingly concerning life-saving medicinal products.
- Finally, these products are channeled to patients through the legal supply chain, whereas they used to be delivered mainly through the Internet.

Under current EU rules, repackaging activities may involve removing the security seal and damaging unique identification codes. These codes are precisely what ensure products traceability. Accordingly, such practices make it even harder to distinguish real medicinal products from fakes.

Moreover, the legal supply chain of pharmaceutical products within the EU often covers actors in different Member States. The legislation therefore needs to have a cross-border aspect, although the Member States may take specific actions. Similarly, it is essential to act both in the intellectual property and public health fields, which is in conformity with the EU policy.

The proposed amendments are as follows:

1. **To identify easily false representation of medicinal products**

   The measure emphasizes safety features ensuring full traceability of each individual package of high-risk products. It creates certain obligations for other players than wholesalers, who act in the distribution chain and are typically involved in the transactions without actually handling the products.

   The proposed new Article 54 0) of the Directive 2001I83IEC reads:

   > "The following particulars shall appear on the outer packaging of medicinal products or, where there is no outer packaging, on the immediate packaging: (0) safety features making it possible to ascertain identification, authenticity and traceability of medicinal products, other than radiopharmaceuticals, subject to medical prescription as defined in Title VI "

   The proposal establishes a prohibition in principle of manipulating safety features on the packaging by actors situated "in-between" the original manufacturer and the last actor in the distribution chain (the pharmacist) or end user (doctor/patient).

2. **To strengthen the control of actors in the distribution chain**

   The proposal completes the minimum requirements lying with the holders of the distribution authorization set down by Article 80:

   > "(e) They must keep records either in the form of purchase/sales invoices or on computer, or in any other form, giving for any transaction in medicinal products received, dispatched or traded at least the following information: date, name of the medicinal product, quantity received, supplied or traded, name and address of the supplier or consignee, as appropriate" (...)
   >
   > "(h) They must maintain a quality system setting out responsibilities, processes and risk management"
   >
   > "(i) They must inform the competent authority of products they receive which they identify as infringing, or they suspect of infringing (...).

   Moreover, in cases where these infringements or suspected infringements relate to a falsified medicinal product, the holder of the marketing authorization or of the trademark that has been falsified shall be informed."

   In the case where the product is obtained from another wholesaler, holders of the wholesaler authorization must verify compliance with good distribution practices ("GDP") of the supplying wholesaler either by themselves or through a body accredited for that purpose by the competent authority of a Member State. Where the product is obtained from the manufacturer or importer, holders of the wholesaler authorization must verify that the manufacturer or importer holds a manufacturing authorization.

   The proposal also provides that the GMP and GDP certificates issued for manufacturers, importers or wholesalers by the Member States will be entered in a Community database managed by the EMEA. An overall picture will be available on this database including positive and negative aspects of any inspection.

3. **Measures concerning active pharmaceutical ingredients (API)**

   The proposal strengthens requirements for import of API from third countries if it could not be established that the regulatory framework in the respective third country ensures a sufficient level of protection of human health for products exported to the ED.

   The proposal's aim is to ensure that the API is of high quality and not falsified.

   Article 46 laying down the obligations of the manufacturer is amended. The holder of the manufacturing authorization will have to use as starting materials only active substances, which have been manufactured in accordance with the detailed guidelines on good manufacturing practice ("GMP") for starting materials. To this end, the holder of the manufacturing authorization will have to verify compliance of the active substances

manufacturer with GMP by itself or through a body accredited for this purpose by the competent authority of a Member State.

Active substances used as starting material shall only be imported if:

- they have been manufactured by applying standards of GMP at least equivalent to those laid down by the Community
- they are accompanied by a written confirmation from the exporting third country that the standards of GMP applicable to the plant manufacturing the exported active substance are at least equivalent to those laid down by the Community, and that the plant is subject to control and enforcement ensuring that those GMP cannot be circumvented.

This last requirement will not apply if the exporting country is listed as third country ensuring a protection of public health equivalent to that in the ED.

The announcement of the creation of new rules governing counterfeiting medicinal products has been warmly welcomed by the associations representing the industry, such as the EFPIA, which had already inspired the impact assessment report published in late 2008. The EFPIA hopes this proposal for a Directive will be voted upon and implemented rapidly.

These three legislative proposals are now due to be discussed before the European Parliament and the Council of Ministers under the ED's co-decision procedure, where the content and detail will be debated.

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