Johnson & Johnson

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Comments on Public Consultation on Pharmacovigilance Legislative Proposals

Dear Dr Arlett,

These comments are submitted by Johnson & Johnson on the public consultation setting forth legislative proposals relating to pharmacovigilance, which was issued by the Commission on December 5, 2007. Johnson & Johnson maintain extensive research and manufacturing operations globally and within the European Union, employ more than 37 000 persons in the EU, and are responsible for some of the leading innovative pharmaceutical and biotechnology medicines.

Johnson & Johnson strongly supports the Commission's efforts to strengthen, rationalize, and harmonize the system of pharmacovigilance in the EU. The EU has taken the lead in many important initiatives relating to pharmacovigilance and in some respects is a model for best practices and standards in the field of pharmacovigilance. Nevertheless, the existing system imposes significant administrative burdens, often resulting from unnecessarily diverse and complex reporting requirements, including duplicative reporting, that will benefit from simplification and harmonization.

The consultation document includes a number of excellent proposals that can enhance the safe use of medicinal products while decreasing administrative burdens for national authorities, the European Medicines Agency (EMEA), and the pharmaceutical industry. Centralized, rapid decision-making on safety issues should benefit patients, improve efficiency, and reduce differences in regulatory requirements among member states. Simplified reporting of adverse drug reactions (ADRs) and provision for less detailed descriptions of pharmacovigilance systems in marketing authorisation applications will lead to consistency, enhance the administrative process and reduce unnecessary administrative burdens for both industry and regulators. More clearly defined responsibilities for both industry and regulators will help increase compliance and protection of public health.

We wish, however, to bring to the Commission's attention a number of specific concerns and suggestions in relation to the consultation document. Our comments are set forth in detail in the attachment to this letter. The following are concerns that we believe are especially important for the Commission to consider as it develops the proposed legislation.

First, the final legislative system must be adequately detailed to ensure harmonized requirements throughout the EU, but should not be unduly prescriptive. Effective pharmacovigilance requires collaboration and interaction among key stakeholders that can be undermined if legislation attempts to prescribe fine details of reporting systems.

Second, the EU must ensure that its requirements are consistent with those developed through international harmonization efforts. In particular, the International Conference on Harmonization (ICH), in which the European Commission is a co-equal party, as well as the Council for International Organizations of Medical Sciences (CIOMS) working parties of the World Health Organization have developed influential documents that assist in maintaining consistent systems for pharmacovigilance on a worldwide basis. Changes should not be made in the EU legislation that depart unnecessarily from agreed international norms.

In addition, we urge the Commission to pay special attention to the following specific issues:

1. The proposed legislation should include provisions designed to address the special pharmacovigilance issues presented by similar biological medicinal products. Draft article 101a of Directive 2001/83 states that "Member States shall ensure that any biological medicinal product prescribed and dispensed in their territory which is the subject of an adverse reaction report is identifiable," but the legislation contains no harmonized system for assuring that this happens in practice. Guidelines issued by the Committee for Medicinal Products for Human Use (CHMP) make clear that such a system is essential for protection of public health, because biosimilars can be associated with adverse reactions that are different from those of the innovative products on which approvals are based.[1] Johnson & Johnson's own experience with increased incidence of pure red cell aplasia due to immunological effects following a seemingly minor change in the formulation of a specific dosage form of erythropoietin underscores the importance of assuring that new biological products are traceable and that suspected adverse reactions are correctly attributed.

   An effective system needs to include three components.
   a. In the interests of accurate product identification, biosimilars should bear distinct nonproprietary names, where scientifically based structural differences can be described, so that products of different manufacturers will be clearly differentiated by a unique product identifier in adverse reaction reports.
   b. Biosimilars should not be substituted for reference products (or other biosimilars) without the permission of the prescribing physician.
   c. Until science advances to a better understanding of the clinical impact of changes to complex biologic medicines, the proposed EU system of intensive monitoring of new medicinal products should routinely be applied to biosimilars for a scientifically appropriate period, so that patients, pharmacists, and physicians are aware of the need for enhanced vigilance.

2. The proposed requirement that all adverse reactions (serious and non-serious) occurring within the EU be reported within 15 calendar days, set out in proposed article 101e(2) of Directive 2001/83, is unworkable as it is proposed. EU law, consistent with the law in other jurisdictions, should distinguish between serious and

[1] Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Non-clinical and clinical issues, section 4.3 (EMEA/CHMP/BMWP/42832/2005)

non-serious adverse reactions. Special attention, including expedited reporting and follow-up, is appropriate for serious reactions, but attempting to give the same priority to non-serious reactions will overburden the system and divert attention and resources from more significant events. We propose that, routinely, non-serious adverse reactions should instead be reported at periodic intervals, on an aggregate basis as occurs today in submissions such as the Periodic Safety Update Report (PSUR). There are two situations where 15 day reporting of all adverse reactions may contribute positively to the public health, and these should be most appropriately defined within product specific risk management plans. Firstly, where there is a need to monitor adverse reactions as part of an identified, or suspected, safety signal at any time during the product lifecycle where expedited reporting of non-serious reaction will benefit the public health. Secondly where a product may be approved at an earlier stage of development and as part of a conditional approval whereby in consultation with the manufacturer additional safety information is required to be collected to complete the product profile. It should be noted that these should be considered exceptions and be product-specific.

3. Consistent with current EU law (and the practice in the United States and other non-EU jurisdictions), evaluation of the benefit-risk balance for medicinal products should continue to focus on the normal conditions of use. Provisions in proposed articles 116 and 117 of Directive 2001/83 that would eliminate this requirement should be deleted. Virtually all medicinal products are associated with serious risks when used inappropriately. The essence of the approval process is development of conditions of use that will assure acceptable safety. Failing to consider the normal conditions of use when determining whether to authorize or withdraw a medicinal product disregards a fundamental principle of drug regulation and benefit-risk evaluation.

4. The definition provisions set out in article 11 of Directive 2001/83 should be consistent with ICH guidance. The definition of an "adverse drug reaction" (or "adverse reaction," if that is preferred) should include language relating to doses normally used, and the definition of an "unexpected adverse drug reaction" (or "unexpected adverse reaction") should be retained. Not only will this maintain consistency with international norms that the European Commission and Member State regulators participated in developing but it will assure appropriate focus on key concepts of drug safety: adverse reactions should be evaluated in relation to the normal conditions of use, and special attention should be paid to new events not previously known to be associated with a medicinal product.

5. The proposed legislation should include more detailed procedures and criteria for implementing the requirement for intensive monitoring of new medicinal products, which is briefly described in section 3.2.6 of the consultation document. The proposal should make clear whether the system will apply to all new products, or only to those for which it is determined to be appropriate under product-specific risk-management arrangements, and how long the requirement will remain in place. If the system will apply to all new medicines, regardless of anticipated risks, this should be made clear to patients and healthcare professionals, so that confidence in the safety of new medicines is not undermined. As noted above, in view of the special risks associated with similar biological medicinal products, the proposal should state that those products will be subject to the intensive monitoring system.

6. Attention should be given to practical issues associated with the establishment of the product information database contemplated by proposed article 57(2) of Regulation 726/2004. Detailed guidance should be issued on the format for such submissions, and details relating to format should be agreed and thoroughly tested before submission requirements are made mandatory.

7. Finally, it would be helpful if the role of other initiatives such as the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP; Doc. Ref. EMEA/601107/2007) were clarified in the context of this consultation. It is noted that this activity proposes to enhance pharmacovigilance effectiveness through a European wide network. The specific contribution of this proposed effort should be incorporated into this consultation to allow a system-wide view of proposed enhancements.

Johnson & Johnson appreciates the opportunity to comment on the consultation document. We look forward to participating in future stages of the process and stand ready to work with the Commission in the development of this important legislation.

Yours sincerely

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cc: F. Reekie
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Attachment