Annex

Comments of the Federal Ministry of Health

on the document presented by the European Commission on 5 December 2007

"STRATEGY TO BETTER PROTECT PUBLIC HEALTH BY STRENGTHENING AND RATIONALISING EU PHARMACOVIGILANCE"

in consultation with the

Federal Institute for Pharmaceutical and Medicinal Products (*Bundesinstitut für Arzneimittel und Medizinprodukte*) and the Paul-Ehrlich Institute

The Federal Ministry of Health (*Bundesministerium für Gesundheit – BMG*) welcomes in principle the European Commission's efforts to strengthen and rationalise the EU pharmacovigilance system. In particular, we would like to comment on the desired amendments and other points in respect of Annex I to the above-mentioned document.

1. Directive 2001/83/EC, Article 1(11): Definitions

The proposed amendment to the definition of "adverse reaction" and the intention to require notifications also for minor adverse reactions could, through the large number of notifications this would engender, lead to the danger that signal generation and risk assessment would become more complicated. We therefore take the view that the Directive must provide that:

- the adverse reaction must be notified within 15 days (which has to date applied only to serious adverse reactions), and
- medication errors are to be indicated separately by pharmaceutical companies when notifying adverse reactions so that they can be automatically recognised in the database and differentiated from adverse reactions in the true sense.

In this regard, we also consider that the term "medication errors" needs to be defined.

2. Directive 2001/83/EC, Article 1(13), (16): Deletion of the definitions of "unexpected adverse reaction" and "abuse of medical products"

We consider that the above-mentioned definitions have demonstrated their worth and proved themselves advantageous in the risk assessment and the associated communication. We therefore propose further discussion of the planned deletions.

3. Directive 2001/83/EC, Article 8(3)(ia): Description of the pharmacovigilance system

The description of the pharmacovigilance system should not contain any contact details for the "Qualified Person". Otherwise, slight changes to these details would regularly result in an amendment notice in accordance with the Variations Regulation 1084/2003/EC, which we consider disproportionately cumbersome.

4. Directive 2001/83/EC, Article 11: Completing the information in the SmPC

We welcome the proposal to present prominently in the Summary of Product Characteristics (SmPC) – in the form of "key safety information" – the most important characteristics of the medicinal product and the necessary measures to reduce the risks. It would appear useful to record also information on the dosage here, since this is particularly important for safe use.

5. Directive 2001/83/EC, Article 22: Early issuing of conditional authorisation

The planned provision requires – also in connection with the Commission's comments in Chapter 3.2.1 of the accompanying text – particularly careful checking. The entire issue should be the subject of a wide-ranging expert discussion.

The amendments currently planned could give rise to the misinterpretation that henceforth conditional authorisations could also be issued for medicinal products which have not been sufficiently tested, leading to a fundamental departure from the current thinking that, in so far as possible, applications for authorisation can be made and approved only for medicinal products which have been tested in accordance with the latest medical science. A system allowing only partially tested medicinal products to be authorised on the condition that substantial efficacy and safety tests be carried out **after** placing on the market would pose unacceptable health risks to patients. We could not agree to this and therefore propose that an appropriate form of words be employed to clarify under which circumstances a conditional authorisation may be issued.

6. **Directive 2001/83/EC, Articles 26, 116, 117: Deletion of the ground for refusal "insufficiently substantiated efficacy"**

   Deleting this ground for refusal would deprive the authorities of an important tool for refusing to authorise products of insufficiently substantiated efficacy or for withdrawing them from the market. The reasons for such an amendment – which are not mentioned in the consultation paper – should be discussed in detail.

7. **Directive 2001/83/EC, Articles 31, 36 and 101k: Institution of risk assessment procedures**

   We endorse in principle the intention to simplify by means of Article 101k the legal bases for instituting and regulating more clearly risk assessment procedures at EU level. However, further clarification is needed with regard to which situations require an arbitration procedure in accordance with Articles 31, 36 and 101k. A European risk assessment procedure for nationally authorised medicinal products should be instituted in accordance with the principles of Article 31.

8. **Directive 2001/83/EC, Article 59: Request on the package leaflet that patients report adverse reactions**

   The package leaflet should include a request that patients report observed adverse reactions to the relevant medicinal products authorities (possibly also to pharmacovigilance centres in some EU Member States), in order to ensure with complete certainty that the authorities actually receive all the essential information they need to carry out their risk assessment.

9. **Directive 2001/83/EC, Articles 101d and 101e: Generating and evaluating signals, obligations to report adverse reactions**

   Adverse reactions – particularly in light of the currently proposed definition – will always be influenced by national particularities (such as doctors' prescription habits). The legislation should therefore provide that adverse reactions observed in a Member State are notified **also** to the competent authorities in that country. This guarantees that the authorities' communication network for sharing information on adverse reactions (in the national language) with doctors, pharmacists, patients and pharmaceutical companies is maintained. This is of particular importance to Germany, as the majority of adverse reactions have to date been notified by pharmaceutical companies.

In the same way, adverse reactions observed in another Member State should be reported also to the competent authorities in the Member State which was the rapporteur or reference Member State for the medicinal product in question.

The provisions concerning what reports are to be prepared by the pharmaceutical companies and then notified to the competent authority require further clarification. It seems questionable whether a significant overview of the adverse reactions to medicinal products on the market can be obtained when it is the pharmaceutical companies alone which ultimately decide whether or not a report is written and notified. It is of primary importance whether healthcare professionals or patients have assumed a link between the use of a medicine and an adverse reaction.

The sole criterion of a temporal connection as a condition for an adverse reaction notification would give rise to "event reporting", which would mean that responsibility for evaluating the contents of individual case reports – above all with regard to the causal relationship – would be transferred from those required to report (pharmaceutical companies) to the competent authorities.

We welcome in principle the rationalisation of the recording of reports of adverse reactions from the scientific literature, but consider that, here too, further discussion is needed with regard to the proposed method of achieving this.

10. Directive 2001/83/EC, Article 101f: Submission of periodic safety update reports (PSURs)

Although we broadly endorse the simplification of the preparation of PSURs, we take the view that they should continue to be submitted for generic medicines too. In many cases, the products from manufacturers of generic medicinal products are much more widely used than those of the original authorisation holder. These manufacturers of generic medicinal products therefore have much more experience with regard to the use (and safety) of medicinal products containing certain active substances. The medicinal products authorities would therefore no longer be provided with adequate documentation of practical experience. Instead of the pharmaceutical companies being obliged to submit PSURs, the medicinal products authorities would be obliged to search for relevant information.

In connection with the planned publication of PSURs and corresponding evaluation reports, it should be pointed out that these also contain preliminary, insufficiently substantiated information and statements which have yet to be confirmed or rejected in the light of new

knowledge. Since such publications could lead to uncertainty among the public, we consider an in-depth discussion of this problem to be necessary.

The proposal also provides that, in future, all PSURs are to be submitted to the EMEA, regardless of the type of authorisation. This would therefore also apply to medicinal products with exclusively national authorisation. This does not seem appropriate for medicinal products authorised in only one Member State. PSURs for these kinds of medicinal products should therefore be submitted only to the relevant national authority.

11. **Directive 2001/83/EC, Article 101i: Publication of Risk Management Plans (RMP)**
    The concerns expressed under No 10 regarding the publication of PSURs and associated evaluation reports also apply in respect of the intention to publish Risk Management Plans and the conclusions of the evaluations of PSURs. This matter too requires in-depth discussion.

12. **Directive 2001/83/EC, Article 101l No 1 e: Updating of the Risk Management System (RMS)**
    The RMS should not be updated by the EMEA, but rather by the relevant rapporteur or reference Member State, or when national authorisations are issued by the competent national authority.

13. **Directive 2001/83/EC, Article 117, No 3: Access to medicinal products following distribution restrictions**
    In our view, this provision requires explanation and justification.

14. **Regulation (EC) No 726/2004, Article 57(2): Setting up a pharmacovigilance committee**
    We expressly welcome the setting up of a pharmacovigilance committee, but consider that there is a need for further discussion of the relevant provisions with regard to the committee's capacity to function effectively and its cooperation with the CHMP.