Ministry of Health, Welfare and Sport
Department of Pharmaceutical Affairs and Medical Technology

European Commission
DG Enterprise and Industry
Unit Pharmaceuticals
Attn. Mr. P. Arlett
Wetstraat 200
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Ons kenmerk	Inlichtingen bij	Doorkiesnummer	Den Haag
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Onderwerp		Bijlage(n)	Uw brief
Assessment Community system of Pharmacovigilance			

Dear Mr Arlett,

Please find in this letter our suggestions about the Community System of Pharmacovigilance. We make these remarks in accordance with the view of the Dutch Medicines Evaluation Board.

1. Reporting of adverse drug reactions (ADRs)
A. Currently only unexpected serious ADRs from outside the EU have to be reported, whereas all serious ADRs from inside the EU are reportable. For many nationally authorised medicinal products differences exist between the national SPCs and, therefore, a certain non-EU ADR may be unexpected in one Member States and expected in another. The proposal is not to make a distinction anymore between unexpected and expected serious ADR from outside the EU.

B. All Member States are already obliged to submit all their serious ADR reports to EudraVigilance and all Member States have access to EudraVigilance. Therefore, with regard to products approved through mutual recognition there is no need anymore that marketing authorisation holders report to both the competent authority of the Member State on whose territory the incident occurred and the reference Member State. The latter obligation can be lifted.

C. There is no obligation to report non-serious ADRs to EudraVigilance, whereas non-serious ADRs can be very important to be known to the prescriber and patient. Non-serious ADR are discussed in PSURs and listed in SPCs. As long as EudraVigilance does not contain non-serious ADRs Member States are obliged to maintain a national ADR database and to develop and maintain analytical tools, whereas many Member States will never have similar sophisticated analytical tools as are in place or under development for EudraVigilance. Non-expedited reporting of non-serious ADR to EudraVigilance should therefore be considered. The obligation for Member States to have a system in place to stimulate ADR reporting and to collect ADR reports should remain.

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2. Periodic Safety Update Reports (PSURs)
A. In principle line extension products and generic products, including products authorised through a hybrid procedure, should have the same PSUR submission scheme as the original product. However, there may be safety concerns which warrant a different PSUR scheme for a certain period after registration of the generic, hybrid or line extension product. Thereafter the PSUR submission scheme should be phased in with that of the original product. This should be decided on a case by case basis at the grant of the marketing authorisation.

B. The relationship between PSUR submissions and renewals does not exist anymore in the recently amended legislation. Renewal dates are linked to the registration dates, whereas the PSUR submission scheme is linked to the first date of marketing of the product. As part of a renewal application also a PSUR has to be submitted. This leads to rather complex PSUR submission schemes in the first 5 to 7 years or so after registration. It would make sense to also link the renewal date to the first date of marketing in order to achieve that the renewal application coincides with a regular PSUR submission.

3. Transparency
PSURs contain important safety information in a structured way. In the current legislation it is stated that the EudraVigilance ADR database should be publicly accessible one way or the other. The next logical step is to also make PSURs publicly accessible. There cannot be a reason to withhold safety information from the general public.

4. Enforcement of Risk Management Plans / Post Marketing Safety studies
The competent authorities do not have appropriate legal tools to enforce Risk Management Plans. Suspension of a marketing authorisation in the case that certain Post Marketing Safety studies are not conducted is not a proper tool, not in the least because it has the adverse effect that patients who benefit from the product are affected, as well as the marketing authorisation holder.

5. Referrals to CHMP
Where a referral of a safety issue to the CHMP concerns a therapeutic class or a range of products containing the same active substance, the procedure can be rather cumbersome due to the number of pharmaceutical companies involved. Marketing authorisation holders of generic products do not normally add much to the scientific discussion. It should be considered to involve primarily only innovator companies in referral procedures. Generic conpanies could be involved on their request. For holders of a hybrid marketing authorisation a case-by-case decision should be taken. The final decision for the innovator products would of course apply to the corresponding generic (and hybrid) products as well.

6. Communication
Currently marketing authorisation holders may not communicate information relating to pharmacovigilance concerns to the general public without giving prior or simultaneously notification to the competent authority. Experience has learned that simultaneous notification to the competent authorities is too late. The competent authority should be informed in advance to be able to propose amendmends of the proposed communication and to make arrangements for own communications.

7. Impact of regulatory actions
Marketing authorisation holders should check systematically the impact of regulatory actions, e.g. the introduction of certain restrictions in the SPC, and report the outcomes to the competent authorities. (Is the goal of the action reached?).

8. Stimulation of reporting of ADRs from medicinal product use in children or off-label
The Commission should publish/sponsor a communication directed at health care professionals about the importance of reporting adverse drug reactions. In particular the knowledge about ADRs related to medicinal products used in children or off-label would benefit largely of an improvement of reporting. In this communication it should be emphasized that reports regarding the use of a medicinal product outside the scope of SPC (off-label) could even be more important than reports related to the authorised use. An element of the communication could be that reports of ADRs will never be used as basis of an assessment of professional conduct; the competent authorities for ADRs will keep the information for regulatory use only.

I would greatly appreciate if you would consider our suggestions.

Yours sincerely,

H.R. Hurts, MA
Director of Pharmaceutical Affairs and Medical Technology