Notification of Safety Concerns (in particular Section I.8)

I. Introduction

The current review of Volume 9 offers an opportunity to clarify the requirements on a marketing authorisation holder (MAH) for forthwith reporting to regulatory authorities in Europe new information that might influence the evaluation of the benefits and risks of a medicinal product. A revised Volume 9 should provide clear guidance on *what* new safety concerns need to be notified, *when* such information should be reported, and *how* it should be reported.

These suggestions are not intended to have any impact on the recently amended EC pharmaceutical legislation (Regulation 726/2004 and Directive 2001/83/EC).

II. Definitions

Safety concern: : New safety information which upon initial analysis, at least to the level of a preliminary assessment report, suggests to be of such significance that a label change or more significant regulatory action may be needed. As proposed below, safety concerns can be further categorized by their level of public health or benefit-risk impact, which in turn translates into urgency and preferred method of notification of the concern. As is clarified in the next definition, a 'signal' is NOT synonymous to a 'safety concern'. The term 'safety concern' can be seen as synonymous to 'new safety information *which might [probably] influence the risk-benefit evaluation of a medicinal product*', i.e. there is at least initial an assessment report.

Signal: Any new safety information which for whatever reasons is considered worth further analysis. A signal may be a single adverse reaction report or series of reports (e.g. through automated signal detection on the safety database), but could also be a question from a health professional or regulatory authority, or the result of a preclinical or clinical study. As such a signal is no more than a question whether there may be a 'safety concern'. Further analysis is needed, at least to the level of a preliminary assessment report, before a signal can be considered a 'safety concern'. The term signal can be seen as synonymous to 'new safety data *which has not yet been further analysed*''.

III. Executive Summary

The current review of Volume 9 offers an opportunity to clarify the requirements on a marketing authorisation holder (MAH) for forthwith reporting to regulatory authorities in Europe new information that might influence the evaluation of the benefits and risks of a medicinal product. A revised Volume 9 should provide clear guidance on *what* new safety concerns need to be notified, *when* such information should be reported, and *how* it should be reported.

The current version of Volume 9a does not properly clarify the text of article 23 of Directive 2001/83/EC as amended and article 16/(2) of Regulation 726/2004:

> ***"[The MAH] shall forthwith inform [the competent authorities] […] of any other new information which might influence the evaluation of the benefits and risks of [the medicinal product] concerned."***

This provision, if not properly clarified in a revised version of Volume 9a, will leave the pharmaceutical industry no choice but to interpret the meaning and for some this will mean reporting all new safety information to the regulatory authorities in an expedited manner. That will overburden the system and risk not responding in a timely fashion to serious safety concerns.

We propose clear definitions for *'signal'* versus *'safety concern'* (see Definitions above), and a categorisation based on the level of risk-benefit impact linked to reasonable timeframes for and methods of notification (see Decision Tree below). The suggested approach will present

regulators with all new safety information that is relevant to the evaluation of benefits and risks of a product within an appropriate timeframe and by means of an appropriate route.

IV. Discussion

EC law requires that a MAH supply the competent authority with any new information that might entail the amendment of various particulars or documents that comprise the dossier and marketing authorisation, including information which might influence the risk-benefit evaluation of a medicinal product. This requirement is set out in Article 23 of Directive 2001/83/EC, as amended by Directive 2004/27/EC and in Article 16(2) of Regulation 726/2004. A similar requirement is included in Article 15(2) of Regulation 2309/93:

> ***"[The MAH] shall forthwith inform [the competent authorities] […] of any other new information which might influence the evaluation of the benefits and risks of [the medicinal product] concerned."***

This provision, if not properly clarified in a revised version of Volume 9a, will leave the pharmaceutical industry no choice but to interpret the meaning and for some this will mean reporting all new safety information to the regulatory authorities in an expedited manner. That will overburden the system and risk not responding in a timely fashion to serious safety concerns. The reasons are as follows:

1. The Oxford English Dictionary defines the term forthwith as "immediately; without delay"; and
2. "Any other new information which *might* influence the evaluation of the benefits and risks of the medicinal product" by definition would include *all* new safety information because any new safety information upon full investigation *might* impact the evaluation of the benefits and risks.

Efforts by pharmaceutical companies to comply with this provision could lead to 'data dumping' with no added value. Such excessive reporting is not only burdensome for pharmaceutical companies and regulators but primarily could lead to serious safety concerns being missed among the noise of other reports.

For this reason we believe it is critical to distinguish a 'safety concern' (*any new safety information which might [probably] influence the evaluation of the benefits and risks of the product*) from a 'signal' (*any new safety information [for which the impact on the risk-benefit of the product hasn't been analysed yet]*). Only safety concerns should qualify for regulatory reporting from the MAH to the authorities, and vice-versa as appropriate.

Single case reports or e.g. automatically generated signals generated from the safety database as such never constitute a 'safety concern', at most new safety information for which an analysis has to be considered. During a given time period there may be numerous signals, many of which are spurious and not requiring (new) analysis reports. There is not added value in the immediate notification of all signals.

There is also a need to better define the terms 'forthwith' or 'immediate', which occur in the legislation and on numerous occasions in Volume 9a. It is of little value to send in all new 'safety concerns' on a 24/7 basis if most of those concerns then require many weeks or even months of assessment by MAH and regulatory authorities before resulting in a factual change to the conditions of use of the medicinal product. The categorization, timing and method of notification of new safety information to the competent authorities should be governed by the clinical significance and potential public health impact of the safety concern. Important safety concerns should be submitted within a reasonable timeframe after initial analysis.

The 'Lectric Law Library's Legal Lexicon' (http://www.lectlaw.com/def/f135.htm) and other legal dictionaries on the Internet define *forthwith* as *"As quickly as reasonably possible. When a thing is to be done forthwith, it seems that it must be performed as soon as by reasonable exertion, confined to that object, it may be done. This is the import of the term; it varies, of course, with every particular case."*. I.e. the legal interpretation of forthwith would suggest

addition of *'reasonable'* to the immediate or urgent aspect of the literal meaning. We believe the proposal to link the seriousness category of the safety concern to reasonable timeframes properly interprets the legal text. Our proposal qualifies 'forthwith' from a public health perspective and thus avoids overburdening the system to such a degree that serious safety concerns are not appropriately responded to.

V. Proposal

The issue as set out above should be addressed in a revised Volume 9a. The requirements should be clarified so that MAHs know exactly what their reporting obligations are regarding the notification of 'safety concerns'. This would enable MAHs to submit to competent authorities, in a timely fashion, all information that is relevant for the evaluation of benefits and risks of a medicinal product.

In order to achieve these objectives we suggest that a revised Volume 9a clarifies what constitutes a '*safety concern'* versus a *'signal'* (see Definitions).

Volume 9a should include a decision tree which categorizes safety concerns by seriousness of the public health impact or impact on the risk-benefit evaluation, and links the categories to different levels of urgency and methods of notification. Examples could be included which support broad understanding of the intent of the categories.

It should be recognized that not every conceivable iteration of safety concerns can be predicted or will fit perfectly into such a decision tree. Therefore there should be clear advice, on how MAHs can rapidly communicate with regulatory authorities to clarify where to place an unusual safety concern in such a decision tree.

For the determination of compliance with the proposed timelines for notification day 0 should always be the date on which at least a preliminary or prefinal draft assessment report is available which allows a tentative conclusion to be drawn by either the MAH or the competent authority, depending upon who is analysing new information.

Decision tree

A first proposal for a decision tree (including some examples for each category) could be:

- **Serious public health issues** (resulting in limitation of availability, or urgent changes to the indications, dose, contra-indications or warnings sections of the SPC)
  - **Critical safety concern (maximum 7 days):**
    - Immediate deaths may frequently occur if no action taken (e.g. product tampering, serious product defect)
      - Notify immediately upon recognition by urgent means (e.g. email, fax, teleconference; if necessary use emergency phone numbers) AND take immediate action (no need to wait for confirmation of notification/ Documentation supporting the need for action could be limited to a single page summary of information and conclusions. First notification of such critical concerns should normally require less than the maximum time of 7 days mentioned.
  - **15 day safety concern:**
    - Significant over-mortality (e.g. in clinical trials) / frequent serious ADRs within indication (and panic discontinuations without proper medical switchover to alternatives may also cause serious harm)
    - Over-mortality / frequent serious ADRs with experimental / off label use, but this use is known to occur in the marketplace
    - Newly recognized very rare serious ADRs where rapid dissemination of information may significantly impact on either frequency, treatment or complications of the ADRs

        - Notify within 15 calendar days of recognition by rapid means (e.g. registered letter, fax, email) AND propose further steps (e.g. Urgent Safety Restriction, or rapid type 2 variation).

- **Limited public health impact**
    - **60-day safety concern:**
        - Statistical over-mortality / more frequent serious ADRs with experimental / off label use, but events are rare and this use is not known to occur with any frequency in the marketplace
        - Newly recognized serious ADR with probably (very) low frequency and/or limited impact expected from urgent communication on frequency / prevention / way ADR is treated.
            - Notify within 60 days by e.g. registered letter or couriered report, and propose for further steps and timeframes (e.g. timeframe for submission of a type 2 variation)

    - **Not major public health impact** (usually resulting only in changes in the Undesirable effects section of the SPC)**:**
    - **6-month safety concern:**
        - New confirmed (non-serious) ADRs without significant impact on benefit-risk assessment, prevention of ADR, treatment of ADR, etc
            - Notify within 6 months, either in the next PSUR or as a type 2 variation by normal means.

In all cases the initial notification or submission, if it did not include this, shall be followed up by a completed evaluation report that shall be submitted to the competent authorities within an agreed timeframe.

Negative conclusions after proper assessment of new safety information (i.e. signals which have been properly analysed and concluded to not represent safety concerns) can be summarized in the next PSUR. Signal analyses which are ongoing at the time of the PSUR can of course also be summarised in the PSUR.

The above is of course a first proposal. Further refinement of such a *'decision tree'* may be needed. However, we believe this decision tree is a good starting point for discussion and detailing of proper and reasonable timings and routes of communication, of properly guiding interpretation of the legal text "*[the MAH] shall forthwith inform [the competent authorities] […] of any other new information which might influence the evaluation of the benefits and risks of [the medicinal product] concerned.".* The proposal will present regulators with all safety information that is relevant to the evaluation of benefits and risks of a product within appropriate timeframes and by appropriate means.