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

***** Comments provided by CSL Behring GmbH *****

Comment on Key Proposals presented in Section 3:

--> Section 3.2.9: "Clearer safety warnings in product information to improve the safe use of medicines"

CSL Behring supports any strategy to improve the safe use of medicines. However, as stated in "A Guideline on Summary of Product Characteristics (SmPC)" duplication of information should be avoided.

All safety data are listed in section 4.8 "Undesirable Effects" of the SmPC.
As defined by "NtA - A Guideline on Summary of Product Characteristics (SmPC), revision 1, October 2005" as well as the latest version of "Quality review of documents for MR/DC/Referral Procedures" (EMEA-QRD templates, version 1.2, October 2006) this section lists all adverse events from clinical trials, post-marketing studies or spontaneous reports. The section is clearly structured to give the user first a general overview and then a detailed listing according to MedDRA classification including the frequency category.

According to this very well structured and understandable presentation there is no necessity to further repeat selective "key" safety information, especially under the aspect to define what – out of the total of listed adverse reactions – will be defined as "key" safety information.
From our perspective these duplications could confuse the reader and will not contribute to a better understanding and an improved compliance.

Comments on the Detailed Proposals to change EU Legal Texts presented in Section 4:

--> ANNEX 1, Directive 2001/83/EC, Article 11, Paragraph 3b:
'Key safety information about the medicinal product and how to minimize risks …..'

Section 3 of the SmPC is exclusively dedicated to the description of the "Pharmaceutical Form". Thus, this section is not the right place to insert information on the safety of the product. Safety data should be placed where it is required according to "NtA - A Guideline on Summary of Product Characteristics (SmPC), revision 1, October 2005" as well as "Quality review of documents for MR/DC/Referral Procedures " (EMEA-QRD templates, version 1.2, October 2006), this means under section 4.4 "Special Warnings and precautions for use" or 4.8 "Undesirable effects".
Please also refer to our comment above regarding section 3.2.9.

--> ANNEX 1, Directive 2001/83/EC, Article 59, Paragraph 1 (ba):
'Key safety information about the medicinal product and how to minimize risks. This information shall be presented in a box surrounded by a black border…..'

As already pointed out above there is no need to duplicate safety information which is already represented in the package leaflet and SmPC in a clearly structured and understandable way as requested and defined by the respective European guidelines.
Thus, there is no need to insert an additional black box repeating the key safety information as already given under section 4. "Possible side effects" of the package leaflet.
In addition, to insert beside a blue box also a black box in the package leaflet will certainly be confusing for the reader and will not lead to a better acceptance of the leaflet (and medicine?) and might not improve the compliance of therapy.

The company, however, in general supports the addition of a sentence that "suspected adverse events should be immediately reported to the MAH" but would prefer to insert this sentence under section 4.8 "Adverse events" (SPC) and 4. "Possible side effects" (PIL), respectively.

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

***** Comments provided by CSL Behring GmbH *****

---> ANNEX 1, Directive 2001/83/EC (Articles 101-108) 'Pharmacovigilance' to be replaced with the following text (with ....), Chapter 4, Article 101e, Paragraph 2:

a) Proposed Article 101e, Paragraph 2 specifies that MAH should submit electronically to Eudravigilance no later than 15-days following the receipt of the report
- ***all adverse reactions*** *that occur in the Community, and*
- *all serious adverse reactions that occur outside the Community.*

It is very much appreciated to simplify the complex reporting rules for single ADR reports.

However, our question/comment relates to the ***non-serious*** *ADRs that occur in the Community*, i.e. whether the proposed changes to put such cases also under the *expedited 15-day reporting rule* is intentional. If yes, this may again put additional burden on MAHs in terms of priority handling and processing of the non-serious ADRs, especially for companies with high volume of non-serious reports.

In addition, it should be specified that the 15-day reporting rule refers to 15 *calendar* days.

b) With regard to reporting responsibilities of MAHs to Eurdavigilance we would like to make the following suggestion:
In order to avoid duplicates in Eudravigilance, MAHs should not be required to submit to Eurdavigilance ADRs they received from a Member State Authority (for ADRs that occur in the Community).

---> ANNEX 1, Directive 2001/83/EC (Articles 101-108) 'Pharmacovigilance' to be replaced with the following text (with ....), Chapter 7, Article 101l, Paragraph 4:

If our interpretation of proposed Article 101l, *Paragraph 4 e)* in connection with Paragraph 4 a) and 4 b) is correct, it adds considerably broader/more complex responsibility to the QPPV's current tasks and responsibilities with regard to the MAH's "risk management system", *while currently applicable Vol. 9A, Part I, Paragraph 1.2.2 provides only for the following:*

"The Marketing Authorization Holder should ensure that the QPPV has sufficient authority

- .....
- *to* ***provide input*** *into the Risk Management Plans and into the preparation of regulatory action in response to emerging safety concerns (e.g. variations, urgent safety restrictions, and, as appropriate, communication to Patients and Healthcare Professionals).*"

It is suggested:

- **To delete the 2nd half of the 2nd sentence in Paragraph 4 a) that reads "which shall cover the tasks listed in this paragraph." This 2nd half of the sentence implies / may imply that the QPPV is also considered responsible - on behalf of the MAH - for the task listed under Paragraph 4 e), i.e. for maintaining and following the risk management system for the medicinal product including all risk minimization measures included in the risk management system and the marketing authorisation.**

- **To delete the 2nd half of Paragraph 4 b) which reads "which shall cover the tasks listed in this paragraph." This 2nd half of the sentence implies / may imply that the pharmacovigilance system, for its establishment and maintenance the QPPV is responsible for (refer to Paragraph 4 a), covers the tasks listed under Paragraph 4 e), i.e. the maintenance and following of the risk management system including all risk minimization measures included in the risk management system and the marketing authorisation.**

Justification for the proposed changes:

Paragraph 1.2.2 of Vol. 9A, Part I most appropriately considers that the MAH's risk management systems for its authorized medicinal products comprise various activities, processes and responsibilities which go far beyond the actual "pharmacovigilance area of responsibility". Some of them are already mentioned in that Paragraph but another example, i.e. the planning and conduct of post-authorization (safety) studies (whether interventional or non-interventional) subject to product specific risk management plans should be mentioned as well.

Within the organizational structure of pharmaceutical companies the establishment and maintenance of risk management systems/preparation of RMPs involves various interacting functions/departments like Preclinical Research, Clinical Research, Medical Affairs, Regulatory Affairs and Pharmacovigilance. Correspondingly the risk minimization activities detailed in RMPs like variations, urgent safety restrictions, planning and conduct of post-authorization (safety) studies, communication to patients and healthcare professionals etc. fall under the responsibility of various departments like Regulatory Affairs, Clinical Research, Medical Affairs. The QPPV - normally either acting as (1) Global Head of Pharmacovigilance, or in multinational companies headquartered outside of the EU as (2) Head of PV Europe residing at the company's European affiliate (MAH in the EU) - has no empowerment over those functions/departments. **The QPPV can therefore <u>not</u> be responsible for maintaining the risk management system including all risk minimization measures. This should remain - with reference to Vol. 9A, Part I, Paragraph 1.2.2 - a responsibility of the MAH who delegates the related activities/responsibilities to the concerned functions/departments within its organization, but ensures that the QPPV has sufficient authority to provide input.**