Comments on the implementing measures in order to harmonize the performance of the pharmacovigilance activities provided for in Directive 2001/83/ED and Regulation (EC) No 726/2004.

General remarks

Lareb strongly supports most of the proposed measures, especially those measures regarding the involvement of patients, transparency and more efficiency.
However, Lareb has concerns regarding the details in working out the proposals for rules, especially regarding the piling of detailed rules that could frustrate the objectives of the measures.

The proposed measures emphasize mainly on the marketing authorisation holders. Countries have national and regional pharmacovigilance centres, who also deal with signal detection and improvement of pharmacovigilance activities and research. Emphasis on compliance with rules limits the time available for actual signal detection and dissimilation of the signals.

Centralization is another important issue. Signal detection and evaluation are being centralized to a large extent. Signal detection on a national level, close to daily practice and reporters, should also be recognized and stimulated.

Individual case reports are a major contributors to evidence for regulatory measures, both in Europe (see June Raine in 'Pharmacovigilance) and the US (personal information Gerald Dal Pan). Reports and signals primarily describe clinical problems. Next to the development of epidemiological methods, case reports remain important and efforts should be made to improve the methods of clinical evaluation in signal detection. The current proposal relies too much on the statistical analysis of pharmacovigilance databases instead of the evaluation of the clinical aspects.

Consultation item no. 8.
Chapter II D: Quality systems for the performance of pharmacovigilance activities by national competent authorities and EMA

1.7 Resource management
Of course it is important that people working in pharmacovigilance are properly trained and that a sufficient number of competent and appropriately qualified and trained personnel shall be available.

But it is unclear what the core competencies should be. When are you competent and appropriately trained? For the training as well, are there plans for a European certificate for pharmacovigilance? Or who will define the content of the training?
Good training facilities of high quality en good general criteria for quality and competencies are more important than detailed rules.

1.8 Compliance management
(a) evaluate the quality, including completeness of the pharmacovigilance data submitted

(b) assess pharmacovigilance data and process it in accordance with the timelines provided by Directive 2001/83/EC

Although the process is very important, it should be stressed more clearly in (b)that assessment of pharmacovigilance data, means a medical assessment and not only a procedural assessment.

(c) effective communication is an important issue. Also it is important to inform each other as soon as possible (d). However it might not always be possible to inform in 24 hours or less prior

to public announcements in case of actual serious safety issues. So a guarantee can not be requested.

Consultation item No 9
Capter II E. Signal detection and risk identification

Of course work sharing can by more efficient, but more important is: what is more effective. Efficiency is good but must not be our aim. How well we can identify a safety concern must be the aim. Although there are advantages of work sharing, it is important to keep in mind that drugs are used in different manners for different indications (this is mostly an issue with off label use) and maybe also in different patient groups, where the national context is important in interpreting a certain event. Also, in order to receive follow up, you have to work on a national level.
As mentioned in the general remarks: signal detection on a national level, close to daily practice and reporters, should also be recognized and stimulated and continued.

Changed risks/new risks
It is good that the detection of a signal shall be based on a multidisciplinary based approached, but does not necessarily have to be supported by statistical analysis within Eudravigilance.
A signal could be raised, also when this is not supported by Eudravigilance. Issues that are country specific, will likely not be disproportionally present in Eudravigilance but will nonetheless constitute a signal. So the support by statistical analysis within Eudravigilance can support and amplify a signal, but should not be a requirement.

Methodology
Statistical signal detection is deemed as very important in the signal detection process, but one must not forget the value of an individual case or a cluster of cases and their contribution to signal detection. The terms nature and quality of data could incorporate this, but it should be more explicitly mentioned.

Consulation item No 10
Is is not clear what the responsibilities between MAH, EMA and NCA is with respect to signal detection in Eudravigilance.

Signal management procedure
MAHs, NCAs and EMA shall ensure that continuous monitoring of the Eudravigilance database occurs with a frequency proportionate to the identified risk, the potential risk and the need for additional information.
The roles and responsibilities are not clear. For good pharmacovigilance, the persons ultimately responsible for the data-mining in Eudravigilance should not have any financial ties to the products monitored.
It is not clear who will have access to the tracking system.

Annex I
Electronic submission of suspected adverse reactions

It is not possible and adviseble to provide patient identifiable information (page 20, point 4 d. e.). This may not be non-compliant with privacy regulations in different countries.

Annex II
Risk management plans

It should be stated in the new measures that a Risk Management Plan should be completely and easily accessible made public at the moment of marketing authorisation.
