PCIM/11/01 Public consultation on implementing measures for pharmacovigilance

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General comment

I regret the absence of a clear emphasis on the following principles as an introduction to the concept paper:

- At the time of marketing authorisation benefits have been well evaluated, while rare and severe risks have not been
- The marketing authorisation holders (MAH) should be responsible for quantifying ADRs (risks) as they have been responsible for collecting data on efficacy (benefits).
- Evaluation of benefit/risk profile is exposed to being biased as long as resources devoted to the post-marketing survey of risks will be a small proportion of resources devoted to premarketing trials.
- National competent authorities and EMA should be responsible for checking quality and accuracy of both sets of data and providing the overall evaluation of benefit/risk profile

Answers to some specific consultation items.

Consultation item 8

At present a large proportion of notifications of serious severe effects are insufficiently documented to allow any ascertainment. Partial or absence of documentation may lead to under evaluation by considering as “validated” only a fraction of notified cases, or to over evaluation by including “rumors”. That is of special concern for very rare and serious ADRs, where a few errors in ascertainment may impact the overall evaluation of risk.

To promote better documentation, I suggest using *the ratio of adequately documented/ total notified cases of serious ADRs as an important criteria of quality control of case ascertainment by MAH.*

Consultation item 10

Signals have been defined. What is still lacking, and much more difficult to elaborate, is the *definition of a threshold in signal magnitude that should initiate actions (warning, active studies….)*

Consultation item 14. Do you agree with the proposed format and content?

Annex I. Electronic submission of suspected ADRs

Agree, no comment

Consultation item 15. Do you agree with the proposed format and content?

Annex II. Risk management plans

The present format as summary does not allow comments. *Part III (pharmacovigilance plans) and V (Risk minimization measures) should be rather different in content whether premarketing trials raised or not a concern on safety.*

Consultation item 16. Do you agree with the proposed format and content?

Annex III. PSURs

Some side effects because of their nature (e.g. benfluorex related cardiac valves alteration) and/or delayed onset have a very low probability of being spontaneously suspected to be an ADR and be reported as such. *Any a priori suspicion of an unusual risk related to pharmacology or class effect should be considered as a signal*.

Definition of signal should also include some consideration on the threshold of signal that should lead to specific studies (mechanistic, case-control, cohort….).

3. PSURs shall provide an accurate estimation of the population exposed, *INCLUDING ACCURATE % or NUMBER of NEW USERS*. Actually the serious ADRs that are immunologically mediated (e.g. SJS/TEN) occur principally/only in the first weeks of first treatment. Adequate denominator is not the total population exposed but the total number of NEW users

Consultation item 17: Do you agree with the proposed format?

Annex IV. Protocol and reports of studies

Proposed format of report. I can only agree on a format that is obviously referring to Strobe "check-list" for observational studies.

From prior experience I suggest anyhow *more emphasis on study size*. The proposed formulation (point 9.5) is "any projected study size" and "any calculation of the sample size that can…." My understanding of using these "any" is that it implies "if done". I do not anticipate that any kind of observational STUDY on post-marketing events could escape the key issue of a predetermined evaluation of study size. Therefore *adequate determination of the study size should be a key requirement for validation of the protocol.*

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