EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

POST-AUTHORISATION EFFICACY STUDIES

Deadline for Public Consultation: 18 February 2013

Name of Organisation	Country
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1. General Comments

1. The document, as it is focused at the moment, concentrates mostly on imposed PAES and within those on clinical trials. We are aware that recital 36 of Directive 2010/84/EU refers to situations in which PAES may be required. Is "required" equivalent to studies which need to be imposed? To our opinion, "required" does not exclude situations where PAES are conducted voluntarily for good reasons. Therefore, it would be very welcome to also receive some clarification on PAES which are intended by the MAH on a voluntary basis. What could be good reasons and benefits of such studies?

2. There are statements made by regulatory bodies (Germany) that there is not such a thing like a non-interventional PAES as there are always safety data collected and therefore they are always to be seen as PASS. Following this logic, all studies, clinical trials and non-interventional studies, would always fall in the category of PASS as there are always safety data collected.

3. There is more confusion around non-interventional / observational studies than around clinical trials. Therefore, the scope of this delegated act should be widened and all possible scenarios should be covered.

4. We strongly suggest to add a separate section on data quality as this may be a crucial point in the delineation between pre authorisation studies and PAES.

5. We also would welcome some discussion on the prevention of centre selection bias (e.g. whether centres should be identified by a random procedure).

2. Specific Comments on Text

Chapter	Section Paragraph Line	Page No.	Comment	Proposed Change
2	**Consultation Item No 1**	**6**	We do think that bringing forward a delegated non-legislative act will encourage focused dialogue between the CA and the MAHs as clear objectives and rationale are agreed. In particular, it would be absolutely welcome to clarify, by drawing different scenarios, in which situations a PAES would be beneficial. Scenarios should cover • Voluntarily conducted PAES o non-interventional / observational o interventional / experimental • Imposed PAES o non-interventional / observational o interventional / experimental (clinical trial or pragmatic clinical trial) See also General Comment.	
4	**Consultation Item No 2**	**8**	We appreciate the clarification of terms, e.g. “efficacy” and “effectiveness” but we are not sure whether “relative efficacy” is also needed. Effectiveness data must be considered as complementary but not substitutive of efficacy data. Effectiveness data could be obtained primarily by interventional / experimental studies (i.e.: pragmatic controlled trail) and - in some specific circumstances – also by well-designed non-interventional / observational studies conducted with high quality standards. Non-interventional / observational studies are a fundamental instrument in order to: 1) evaluate the safety profile of a medicinal product in the real life and 2) to identity hypotheses to be later validated by interventional / experimental studies (pragmatic or not pragmatic clinical trial).	

			Thus it seems quite appropriate to say that "post authorization efficacy studies" should focus on generating efficacy data or effectiveness data depending on the type of study used (clinical trial or pragmatic clinical trial or non-interventional / observational studies) and depending on the goal of the study. It is of importance to also find scenarios for PAES which are non-interventional / observational. For example, to collect data under real life condition which subsequently will be compared with historic data from pivotal clinical trials. Editorial (section 4, page 7): In par. 1, last line: we would prefer "versus placebo **or** versus ...".	
5	**Consultation Item No 3**	**11**	The last situation (5.7) is probably the more frequent one (change in efficacy/safety due to real life condition) and it is presented as a rare situation. **5.7 Paragraph above the box with** „Moreover, the current guideline on clinical evaluation of vaccines adopted by EMA's Committee for Medicinal Products for Human Use already notes the importance of effectiveness studies in the particular case of vaccines: 'efficacy studies will not always be feasible. For some antigens, a possible alternative may be to use estimates of effectiveness from prospective studies conducted during vaccination campaigns after authorisation in order to establish at least putative correlates for short and/or long-term protection'…." It is confusing that suddenly there is a switch to effectiveness studies. If an efficacy study is not feasible, would an effectiveness study still fall under the term PAES? This refers back to Consultation Item Nr. 2.	
5	**Consultation Item No 3**	**11**	EUCROF agrees with the scenarios.	
6	**Consultation Item No 4**	**11**	The use of "interventional" and "not interventional" instead of "experimental" and "observational" studies respectively is strongly misleading and not recommended. See also "ENCePP considerations on the definition of non-interventional trials under the current legislative framework (Clinical Trials Directive 2001/20/EC) dated 22	

			November 2011 In par. 3, “pragmatic trial” cannot be included in “non interventional studies” since a pragmatic trial is experimental in nature. The fact that observational studies and pragmatic clinical trials “have rarely been used as a source of primary evidence” is an argument that needs to be better discussed, since these types of studies should not be considered inappropriate for the measurement of effectiveness. We would definitely appreciate some more details on the design and prerequisites for PAESs, e.g. protocol, sample size determination, data quality. A definition on “pragmatic trials” would be very welcome. (for example in order to clarify that in a pragmatic clinical trial placebo as a control may usually not be applicable).	