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Submission of comments on EC Consultation Paper on delegated Act on Post Authorisation Efficacy Studies - Ares (2012)1405774

Comments from

Name of organisation or individual
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Consultation Item 1: A DELEGATED ACT — WHAT IS THE ADDED VALUE? **Do you think that a delegated act on the situations in which a post-authorisation efficacy study may be required will be of added value and that the Commission should consider bringing forward a draft delegated act? Please provide reasons for your opinion.**
In general, Vaccines Europe believes that for prophylactic vaccines a delegated act on post-authorisation efficacy studies will bring no added value. Moreover, Vaccines Europe believes that for prophylactic vaccines the two paragraphs included in the current legislation on the situations in which PAESs may be required (Article 22a (b) of Directive 2010/84/EU amending 2001/83/EC and Article 9.4. (cc) of Regulation (EC) No 726/2004) should be sufficient to allow regulators to decide on whether a PAES is needed or not. As highlighted in the response to Consultation Item 2, for vaccines there is a specific value to generate effectiveness data and benefit can be deduced from effectiveness studies. In fact, for prophylactic vaccines the concept of post-authorisation effectiveness studies as part of post-authorisation commitments is not new, and existed well before the introduction of the new PV legislation. It is also important to note that guidance on the type of studies that may be required for vaccines in the post-authorisation phase is currently already provided in the Committee for Medicinal Products for Human Use (CHMP) guideline on clinical evaluation of new vaccines (EMEA/CHMP/VWP/164653/2005). Vaccines Europe would therefore like to suggest that prophylactic vaccines are out of the scope of a delegated act on post-authorisation efficacy studies. In the case vaccines would be in the scope of a delegated act, vaccine specificities and existing regulations should be contemplated in a separate section/paragraph. Finally, Vaccines Europe also considers that a delegated act should not provide details on the type of studies that would be required. These details are product specific and need to be agreed on between the MAH and the regulatory agencies on a case-by-case-basis taking into account the specificities of the product.

Consultation Item 2: EFFICACY VERSUS EFFECTIVENESS

Do you have comments on the above?
Do you agree that generally speaking post-authorisation efficacy studies should focus on generating efficacy data?

Vaccines Europe does not agree that post-authorisation efficacy studies should focus on generating efficacy data, and is of position that a delegated act should not dictate the type and methodology of the studies that should be conducted.

On the contrary, for vaccines there is a specific value to generate effectiveness data and benefit can be deduced from effectiveness studies.

There are several examples of vaccines authorised in the EU where effectiveness studies have been performed as a post-approval commitment. Further explanation on this choice is given below.

Specificities of vaccine effectiveness studies
Unlike most medicinal products, the benefit of vaccine effectiveness studies is that they reflect both direct (vaccine-induced) and indirect (population-related) protection during routine use. Thus, for prophylactic vaccines, they provide practical "real world" data and a better estimate of the true protective efficacy of vaccination when introduced in the population under existing clinical practice conditions. Also, herd protection and or indirect vaccine effects are difficult to be measured in efficacy trials. The tool to measure herd effects are post marketing effectiveness studies often part of nationwide disease surveillance. The herd effects can significantly contribute to the benefit of a vaccine, with documented additional disease reductions in the vaccinated and un-vaccinated age groups.

We therefore disagree with the statement that "the large majority of studies will have a clinical trial design" (page 8, last paragraph consultation item 2).

Vaccines Europe would also like to comment on the assumption that: "observational studies are often based on the analysis of patient registries…" (page 7). While this may be true for pharmaceutical products, it is not applicable for vaccines. Controlled randomised trials (CRT) cannot address the indirect, population-level, vaccine effect. Instead, a large variety of study designs are used for effectiveness studies such as observational cohort, case-control, cross-sectional or cluster-randomised controlled approaches. In most cases, these studies are implemented in coordination with public health authorities in countries with the appropriate surveillance and health care infrastructures.

Specific limitations of vaccines to conduct efficacy studies
It is very important to note that for vaccines there are specific limitations with regard to the possibility of conducting efficacy studies in the post-approval phase:

- Reported incidences of infectious disease are often below 30 cases per 100,000 sometimes below 5 cases per 100,000 persons. In that case RCT efficacy trials would result in study sizes above 100,000 subjects and are, therefore, not feasible.
- When a vaccine is recommended in a country and a vaccine for the same disease is already on the market placebo controlled clinical trials are ethically not acceptable, as this may result in excluding a subpopulation from the national vaccination program.

In addition, the European Medicines Agency guideline on clinical evaluation of new vaccines that came into effect in 2007 (EMEA/CHMP/VWP/164653/2005) highlights the importance of well-conducted assessments of vaccines after initial authorisation and a specific section on effectiveness has been included in the guideline. Section 4.2.2 of the guideline stipulates that the assessment of vaccine effectiveness can provide useful information in addition to any pre-authorisation estimates of protective efficacy, and that even when it was not feasible to estimate protective efficacy pre-authorisation it may be possible and highly desirable to assess vaccine effectiveness during the post-authorisation period.

Long-term benefit estimates

For prophylactic vaccines long-term benefit estimate at the level of the population cannot be made through efficacy studies. The long-term impact of vaccine use on the distribution of the vaccine preventable infection/disease in the population can be estimated using:

- Impact studies which estimate the overall reduction in the population of the disease burden;
- Surveillance systems that monitor the trends over time in infectious disease epidemiology.

Examples where effectiveness/impact studies are part of the post-authorisation approval commitments in the EU are the rotavirus vaccines, the cervical cancer vaccines and the pneumococcal polysaccharide conjugated vaccines. The risk management plan (RMP) section of Section 5 of the European public assessment report (EPAR) of these vaccines mentions the effectiveness/impact studies that have been committed to at the time of approval.

In conclusion, Vaccines Europe would like to highlight that:

- for prophylactic vaccines the focus should not be on efficacy studies as there is an added value to conduct effectiveness studies (when these studies are justified as there is no other means to obtain evidence regarding the benefit of a medicinal product);
- if a delegated act is issued we believe that it is of utmost importance that the specificities of vaccines are considered;
- finally we believe that in case a delegated act is issued, it should not be prescriptive on the type of study or its design as it remains the duty of scientific experts; also a too prescriptive delegated act would have the risk of not covering exhaustively all possible situations.

Consultation Item 3: SITUATIONS IN WHICH A POST-AUTHORISATION EFFICACY STUDY MAY BE REQUIRED

Please comment on the seven different situations described in the consultation. Do you agree that in these situations, a competent authority may ask for a post-authorisation efficacy study? Are there any other situations not covered in which it would also be justified to oblige a marketing authorisation holder to conduct an efficacy study? If this is the case, could you please elaborate on these situations and, if possible, give specific examples to underpin the need?

Although based on regulatory experience, the seven situations described do correspond to situations in which a post-authorisation efficacy studies may be considered, it is important to note that for vaccines, the benefit of a vaccine in some of these situations can be demonstrated by either performing effectiveness or immunogenicity studies. Whether a post-authorisation effectiveness study needed will depend on the type of vaccine, and needs to be assessed on a case-by-case basis.

Vaccines Europe is of opinion that a delegated act should not go in the details about the situations in which a post-authorisation study should be requested. If the decision would be to provide this kind of details in a delegated act, it would be very important to clarify that a post-authorisation study only should be requested if there are no other means to obtain evidence regarding the benefit of a medicinal product. Also, the feasibility assessment should be an integral part of the decision making process of whether a post-authorisation study should be conducted by the MAH.

In the sections below, Vaccines Europe provides specific comments on the relevant situations for vaccines as described in the consultation paper.

1. Studies aimed at detecting clinical outcome following initial assessment based on surrogate endpoints
Vaccines Europe disagrees that this situation should be described in a delegated act for prophylactic vaccines.
For prophylactic vaccines, when there is an established correlate of protection, efficacy studies are not necessary.
Nevertheless, effectiveness studies could have an added value. This should be identified on a case-by-case basis.

2. Studies on combinations with other medicinal products
Vaccines Europe disagrees that this situation should be described in a delegated act for prophylactic vaccines.
For vaccines it should be taken into account that when additional data are requested in the post-authorisation phase, these concern typically the situations where it is likely that there will be a concomitant use of vaccines. Several childhood immunisation programs in the EU Member States foresee the co-administration of vaccines. It is well accepted, as also described in section 4.3.1 of the CHMP guideline, that concomitant use can be studied through assessment of immune interference.
There are several examples of vaccines where section 4.5 (Interaction with other medicinal products and other forms of interaction) of the Summary of Product Characteristics (SmPC) was amended in the post-authorisation phase based on serological data, to allow co-administration with other

vaccines.

3. Studies in sub-populations
Vaccines Europe disagrees that this situation should be described in a delegated act for prophylactic vaccines.
There are sub-populations (e.g. HIV, different age) for which post-approval commitments have been requested in the past. However, in the vast majority of cases there are immunogenicity studies, as it would not be feasible to conduct efficacy studies in different populations

4. Studies in the context of the European Standard of care
Vaccines Europe disagrees that this situation should be described in a delegated act for prophylactic vaccines.
In particular, Vaccines Europe would like to point out that in many cases there is not a consensus between Member States as to what constitutes the standard of care for in the case of vaccines. That is the case because of the preventive nature of vaccines and the fact that vaccines are only recommended is some countries whereas they are mandatory in other ones.

5. Studies linked to a change in the understanding of the standard of care for the disease and/or the pharmacology of the medicinal product
Vaccines Europe disagrees that this situation should be described in a delegated act for prophylactic vaccines.
In particular, Vaccines Europe would like to point out that in many cases there is not a consensus between Member States as to what constitutes the standard of care for in the case of vaccines. That is the case because of the preventive nature of vaccines and the fact that vaccines are only recommended is some countries whereas they are mandatory in other ones.

6. Studies aimed at determining the long-term efficacy of a medicinal product
Vaccines Europe disagrees that this situation should be described in a delegated act for prophylactic vaccines.
If a delegated act would describe a situation on long-term vaccine efficacy, it will have to take into account vaccine specifics. For prophylactic vaccines it is very important to have an understanding of the persistence of the immune response and the need and timing of booster doses after the primary vaccination.
The CHMP guideline on Clinical Evaluation of Vaccines mentions that (since data may not always be available at the time of the initial marketing authorisation) recommendations for boosting may have to be based on long-term immunogenicity follow-up and/or data on vaccine effectiveness that are obtained during the post-authorisation period, and that therefore plans should be in place for appropriate post-marketing studies.
In practice, the kind of studies that manufacturers have been committing to in the past vary from assessing the persistence of the immune response to amending the planned/ongoing efficacy/effectiveness studies to obtain data on long term efficacy.

7. Studies in everyday medical practice
Vaccines Europe disagrees that this situation should be described in a delegated act for prophylactic vaccines.
As explained in the response to Consultation item 2 when post-authorisation efficacy studies are requested by regulators these are often effectiveness studies that are performed in everyday medical practice. Vaccines Europe notes that for this aspect the EC Public Consultation paper indeed refers to the CHMP guideline on Clinical Evaluation of Vaccines, and recognises that in the case of vaccines the needs for post-authorisation

studies, which focus on everyday medicinal practice, mirrors an existing consensus in the medical community.

Consultation Item 4: STUDY DESIGN

Do you have any comments on the statements outlined in the Consultation?

Vaccines Europe disagrees with the statement that "interventional studies are expected to represent the majority of cases". For vaccines, non-interventional studies have been key to determining vaccine effectiveness. It should not be forgotten that well designed observational studies, especially when the results from them are replicated over time for a given product and outcome by various independent researchers, are not always inferior to pragmatic and observational trials. There is still a place for observational studies in this process, and as electronic medical records, insurance claims, and other large datasets continue to become more widely available, these potentially more cost-effective resources may continue to be a reasonable alternative to trials.

Vaccines Europe agrees that if a delegated act would be issued the aspects concerning the specific design of post-authorisation studies should not be covered in detail. As explained under consultation item 2 this will depend on the type of vaccine and needs to be assessed on a case-by-case basis.

In addition, Vaccines Europe would like to expose a set of reasons for which the delegated act should not cover the specificities of the design as it is the duty of the researchers/investigators/regulators to determine the appropriate designs:

- Different products may require different study designs (e.g. disease surveillance of vaccine failure vs. antibody or other biological monitoring of vaccine efficacy and severity of a disease secondary to vaccine failure)
- Trade off between study designs because of feasibility and ethical considerations of one versus another (e.g. observational studies versus clinical trials for marketed vaccines)
- Propensity score and instrumental variable methods are promising, but they are not widely used or understood by most researchers (with the exception of those at a few academic institutions). These methods should continue to be developed, but not necessarily serve as the only design option for observational epidemiologic studies.

Consultation Item 5: **Please feel free to raise any other issues or make any comments which have not been addressed in the consultation items**
In addition to the points of concern already raised, Vaccines Europe would like to address the following issues regarding the conduct of post-authorisation studies for vaccines: • Finding the right setting and being sure of the proposed study design is a lengthy process that can take up to several years. Therefore we would like to highlight the importance of being able to establish a commitment to come back to the regulatory authority within an agreed time frame with a feasibility assessment and a possible timing and design. • Even if networks exist in countries that could be used to perform effectiveness studies, these may not necessarily agree to collaborate with industry or provide access to data, which is an additional challenge to be taken into account. • There will be a need to foster an environment of public-private partnership to be able to conduct such a study on a timely manner and not jeopardise access to vaccines. • Finally, Vaccines Europe would like to highlight that the major issue with vaccines ¡s not post-marketing authorisation commitments including effectiveness and safety, but perspectives to the future use and role of vaccines in the EU in general.