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Committee for Medicinal Products for Human Use (CHMP)

Questions and answers on the withdrawal of the CPMP Note for guidance on preclinical pharmacological and toxicological testing of vaccines (CPMP/SWP/465)

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Background

The CPMP Note for guidance on preclinical pharmacological and toxicological testing of vaccines was adopted in 1997 (1). No revision of the guideline has taken place after that. There is a need to consider revision of the document.

The WHO plays an important global role in vaccine development. As part of this effort, they have developed guidelines directed to national regulatory authorities and vaccine manufacturers. The WHO guideline on nonclinical evaluation of vaccines (2) was published in 2005 and was the result of a collaboration between experts from different regulatory agencies, health agencies, academic institutions and vaccine manufacturers. EU regulators took active part in this work.

Following discussion within the CHMP Safety Working Party and Vaccine Working Party, it has been agreed to remove the CPMP guideline on preclinical pharmacological and toxicological testing of vaccines, and to refer to the WHO guideline on nonclinical evaluation of vaccines.

The aim of this Q&A document is to provide clarification on the grounds for this decision and the consequences thereof.

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Questions and answers

Question 1. What are the important differences between the EMA and the WHO guidelines?

The nonclinical development program for vaccines has not undergone any major changes since the CPMP guideline came in place. Due to the complex mode of action of vaccines, animal studies are normally the only the possibility to address the pharmacological and toxicological activity of a vaccine. Since vaccines in most cases are given to large numbers of healthy individuals, there is a need for a solid nonclinical safety evaluation.

The nonclinical program outlined in the WHO guideline is therefore largely in agreement with the program described in the EU guideline. There are a few differences with the WHO guideline bringing some further clarity and there are cases where the WHO guideline describes a more restrictive animal use with no consequences for the safety evaluation. Thus, according to the WHO guideline there is no need for dedicated studies on safety pharmacology but these endpoints can be included in repeat dose toxicity studies. Also, there is no need for single dose toxicity studies but a study on repeat dose toxicity may suffice.

Question 2. Are there any legal consequences by referring to a non-CHMP guideline?

No. A CHMP guideline does not have legal force. As written in the EMA document describing the status of scientific guidelines: “Scientific guidelines are to be considered as a harmonised Community position, which if they are followed by relevant parties such as the applicants, marketing authorisation holders, sponsors, manufacturers and regulators will facilitate assessment, approval and control of medicinal products in the European Union. Nevertheless, alternative approaches may be taken, provided that these are appropriately justified.” (3). Therefore, by referring to the WHO guideline, the same principles apply.

EMA/CHMP does not have the possibility to directly introduce changes in a WHO guideline. However, since WHO is an international body and this guideline was developed with the participation from regulators from EU and other regions, it is believed that this guideline will continue to reflect a global and harmonized position, also when there is a need for revision of the guideline.

Question 3. Are there any differences in the scope of the guidelines?

The two guidelines have a similar scope. Both guidelines are limiting the scope to products intended to induce a specific, active and protective host immunity against infectious diseases. It describes the active components of vaccines: inactivated microorganisms, attenuated live microorganisms, antigens extracted from microorganisms, secreted by them or produced by recombinant DNA technology. In contrast to the EU guideline, the WHO guideline also includes vaccines containing a live vector or nucleic acid. This is considered appropriate since many of the nonclinical aspects to be addressed are common for traditional vaccines and vaccines containing a live vector or free DNA. Specific aspects to be addressed in these cases are described in other guidelines (4).

The WHO guideline includes therapeutic vaccines for infectious disease indications in the scope. This is not mentioned in the EU guideline. It is agreed that to a large extent, the nonclinical program would be similar in this situation.

Both guidelines clearly indicate that therapeutic vaccines for non-infectious disease (e.g. certain cancer vaccines) and monoclonal antibodies uses as immunogens (e.g. anti-idiotypic antibodies) are not covered by these guidelines.

Question 4. Is the 3R perspective taken care of in the WHO guideline?

As discussed in the answer to Question 1, animal experiments are considered pivotal for the development of vaccines. Nevertheless, all efforts should be taken to limit the number of animals and the impact on well-being in animals. As earlier mentioned, the WHO guideline gives clear opportunities for limiting animal use as compared to the EU guideline. There is no need for stand-alone safety pharmacology studies, and there is no need to perform single dose toxicity studies.

References

1) CPMP Note for guidance on preclinical pharmacological and toxicological testing of vaccines. CPMP/SWP/465

2) WHO guidelines on nonclinical evaluation of vaccines. WHO Technical Report Series, No. 927, 2005

3) Status of EMEA scientific guidelines and European Pharmacopoeia monographs and chapters in the regulatory framework applicable to medicinal products. EMEA/42371/2008

4) Guideline on the non-clinical studies Required before first clinical use of gene therapy medicinal products. EMEA/CHMP/GTWP/125459/2006