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Committee for Medicinal Products for Human Use (CHMP)

Concept paper for a guideline on the quality of porcine trypsin used in the manufacture of human biological medicinal products

Agreed by BWP	13 July 2011
Adoption by CHMP for release for consultation	22 September 2011
End of consultation (deadline for comments)	31 December 2011

Comments should be provided using this template. The completed comments form should be sent to Dolores.Hernan@ema.europa.eu

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1. Introduction

Porcine trypsin is a common reagent used during the manufacture of biological medicinal products for the detachment of cells from the culture vessel for their passage. At manufacture of some vaccines, trypsin is added to the final culture stage at virus production for activation of the virus. In addition, for the manufacturing of specific recombinant proteins (e.g. insulin), trypsin is used as a reagent during the downstream process.

2. Problem statement

Porcine trypsin, being an animal derived material manufactured from the pancreas of pigs, carries the risk of contamination with adventitious agents. This may especially be the case for certain viruses which are widespread among pigs and which are difficult to eliminate due to their high resistance against physicochemical treatment.

3. Discussion (on the problem statement)

Animal-derived materials can be contaminated with a wide range of biological agents and therefore it is strongly recommended that all these materials are appropriately selected, tested and treated for the inactivation and/or elimination of such agents before they are used at manufacture of medicinal products. Contamination of pharmaceutical facilities with adventitious viruses may lead to a shutdown of production and to supply shortfall. Contamination can also alter growth properties of cultured cells and, theoretically, this could lead to altered properties of a biological product. For medicinal products where no virus inactivation is possible at down-stream processing steps (e.g. live vaccines) or where, in addition, testing for contaminants at the end of production is difficult (e.g. some cell based medicinal products), well-controlled cell culture reagents are essential to avoid exposure of patients to adventitious viruses.

Early in 2010 Victoria *et al.* reported the finding of DNA sequences of porcine circovirus in a live attenuated rotavirus vaccine. Further, investigation confirmed contamination with PCV and revealed that the origin of PCV contamination could be attributable to the porcine trypsin used in the manufacture of the vaccines.

Although specific Guidance has been given for bovine sera used as cell culture reagent in manufacture of human medicinal products (CPMP/BWP/1793/02), to date no guidance has been given for porcine trypsin.

4. Recommendation

As a result of the PCV DNA findings in live attenuated rotavirus vaccines the CHMP recommended the drafting of a guideline on porcine trypsin.

The following aspects will be addressed: scope of the guideline, types and source of porcine trypsin, manufacture and preparation of batches, tests for identity, purity and suitability for cell culture, testing for adventitious viruses, tests for sterility, virus reduction methods, quality system, certificate of analysis, regulatory implications.

The guideline should consider potential contaminants of porcine pancreas as source material usually obtained at routine slaughtering. Appropriate strategy for selection of source material and testing strategies as well as test methods for these contaminants should be outlined.

Selection and testing is always associated with limitations with respect to exclusion of biological contaminants. Therefore, specific attention will be given on methods for inactivation/removal of pathogens. The guideline should define appropriate targets for inactivation/removal of potential virus contaminants and outline the strategies for validation of such steps (e.g. use of appropriate model viruses).

During the drafting of the guideline consideration will be given to whether already-authorised medicinal products, as well as new ones, should fall within the scope of this guideline.

5. Proposed timetable

A drafting group has been formed, which can meet at dedicated drafting group meetings, in the margins of the BWP and via TC. It is aimed that a guideline for consultation can be adopted in the first half of 2012 by BWP/CHMP, followed by a 6- month consultation period.

6. Resource requirements for preparation

A BWP drafting group has been formed, which can meet on the margins of the BWP meetings. In addition, discussions can be taken forward progressively through other means (email correspondence, Vitero meetings if necessary). One rapporteur has been appointed.

A discussion meeting with manufacturers of trypsin and other interested parties such as producers of medicinal products might be beneficial. This could be after publishing the draft guideline and public consultation.

7. Impact assessment (anticipated)

- Benefit for industry: avoiding cell culture contamination events. Guidance on sourcing of raw material (reagent).
- Benefit for patients: Avoiding exposure or infection with cell culture contaminants. Avoiding supply issues due to shutdown of contaminated facilities.

8. Interested parties

- manufacturers of biotechnological medicinal products,
- manufacturers of porcine trypsin and manufacturers of alternative reagents.

9. References to literature, guidelines, etc.

- ICH Q5A: ICH harmonised tripartite guideline on Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin
- Victoria JG, Wang C, Jones MS, Jaing C, McLoughlin K, Gardner S, Delwart EL. Viral nucleic acids in live-attenuated vaccines: detection of minority variants and an adventitious virus. *J Virol*. 2010 Jun;84(12):6033-40
- WHO recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products and for the characterization of cell banks (2010).
- Note for guidance on virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses (CPMP/BWP/268/95).

- Note for guidance on the use of bovine serum in the manufacture of human biological medicinal products (CPMP/BWP/1793/02).
- European Pharmacopoeia 7.1- General text 5.2.3 on cell substrates for the production of vaccines for human use.
- European Pharmacopoeia 7.0. Bovine serum monograph.