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Guideline on the adventitious agent safety of urine-derived medicinal products

Draft

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This guideline replaces the document on Biological products derived from human urine (CPMP/118/95).

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

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Guideline on the adventitious agent safety of urine-derived medicinal products

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1. Introduction (background)

Human urine is used to prepare several products indicated in the field of endocrinology, such as human chorionic gonadotropin (hCG), human menopausal gonadotropin or menotropin (HMG) and follicle-stimulating hormone (FSH) and urokinase products used for thrombolysis. These hormones and urokinase extracted from pooled human urine were available on the market as early as the 1970s. Significant improvements in the manufacturing processes of these products have been introduced in the 1990s in order to reach a higher purity profile. In parallel, marketing authorization dossiers have been updated as regards the viral safety standards set during this decade.[1] Urine may be naturally contaminated with viruses harboured in the urinary tract. Other viruses arising from the genital or intestinal tract during urine collection may be present in urine donation. Assessment of the viral clearance capacity of manufacturing processes has shown that the purification processes of these medicinal products contain several steps able to remove/inactivate adventitious agents. These data provide support that the viral safety record for this class of products is largely due to the extraction and purification processes.

The emergence of variant Creutzfeldt-Jakob disease (vCJD) in the 1990s and more recently the cases of apparent iatrogenic vCJD infection by blood transfusion in man in the UK prompted EMA to assess the risk linked to the use of urine-derived products as regards this new form of CJD. Expert meetings addressed this question in 2002 and 2007[2] and the results of these assessments were included in the Position statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products and its revisions (February 2003, June 2004 and June 2011).[3]

2. Scope

Medicinal products derived from human urine fall under the definition of Article 1(2b) of Directive 2001/83/EC[4] as follows: “Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.”

This document addresses specific aspects which should be taken into consideration in the evaluation of viral and TSE safety of medicinal products derived from human urine.

3. Legal basis

This guideline should be read in conjunction with the introduction and general principles (4) and Annex I to Directive 2001/83/EC as amended.[4]

4. Adventitious agents safety

4.1. Selection of donors

Generally, donations of urine are from volunteers, who are instructed to refrain from donating in case of illness. In addition, for enrolment in a donor panel, manufacturers should establish exclusion criteria with respect to the general status of health as far as this is feasible. Accordingly, for urine-derived hormones, which are sourced from a relatively small well-defined donor population, manufacturers have put in place limited exclusion criteria for the selection of a donor. However, for other products manufactured from very large donor pools (e.g. urokinase), such measures are difficult to apply.

As urine collection takes place outside of professional supervision these criteria would not be checked at each donation unlike blood/plasma donors. Therefore manufacturers should follow up the donor criteria at defined intervals.

4.2. Processes

Two classes of drug substance are derived from human urine - hormones (hCG, hMG, FSH) and urokinase. Manufacturing strategies vary according to product and manufacturer. They generally consist of extraction, precipitation and purification steps, which are applied after individual urine collections, with or without preservative, have been pooled.

Urine may be contaminated with viruses harboured in the urinary tract or with viruses originating from the genital or intestinal tract. Taking into consideration limitations associated with testing of large urine pools used as starting material, virus safety mainly relies on the potential of the production process to inactivate or remove viruses. Manufacturers are therefore required to investigate the capacity of their manufacturing processes to inactivate/remove a broad range of viruses representing various physico-chemical properties. The available data suggest efficient clearance of viruses, which may contaminate the urine pool, by defined steps in the manufacturing process. More specifically, for urokinase dedicated viral clearance steps often consist of a pasteurisation step and nanofiltration. As regards the urine-derived hormones, virus clearance is attributed to a combination of process steps, which are specific for the individual manufacturing processes, such as alkali treatment, precipitation or chromatographic steps. Manufacturers of urinary-derived hormones have been encouraged to incorporate nanofiltration to further improve clearance of highly resistant, small non-enveloped viruses and several manufacturing processes include such a virus filtration step.

Due to the number of places where starting materials are sourced, particular attention should be given by manufacturers to the overall Quality Assurance System in place for the whole collection system and to the validation/control of the early production steps of the manufacturing process.[7]

4.3. Investigational studies of inactivation/reduction capacity of the manufacturing processes

General guidance on choice of viruses is given in the *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, revised).[1] This section contains further guidance relevant to urine derivatives. The viruses that are the more frequently found in human urine are hepatitis B virus (HBV), human cytomegalovirus (HCMV), and those from papillomavirus and polyomavirus genus. The presence of other viruses brought by faecal contamination cannot be excluded (e.g. hepatitis A virus (HAV) or other enteroviruses, hepatitis E virus (HEV), adenoviruses, noroviruses, astroviruses, coronavirus-like particles, rotaviruses).

Viruses to be used in validation studies on urine-derived medicinal products should include:

Enveloped viruses

- enveloped RNA viruses (e.g. bovine viral diarrhoea virus (BVDV))

Enveloped RNA viruses such as rubella virus, mumps virus or measles virus are shed into human urine during acute infection. RNA from numerous additional enveloped viruses has been detected in human urine. Even if the presence of infective enveloped virus particles in urine is unlikely in many cases, it cannot be totally excluded. Various enveloped RNA-models have been used to validate virus inactivation methods. However, to date, the pestivirus bovine viral diarrhoea virus (BVDV) is considered as a worst-case model for other RNA enveloped viruses.

- enveloped DNA viruses (e.g. herpesvirus, pseudorabies virus (PRV))

Human cytomegalovirus (HCMV) can be transmitted via urine. It is recommended to include a herpesvirus such as pseudorabies virus (PRV) in the panel to model DNA enveloped viruses. For the validation of steps based on size exclusion (virus filtration) studies with herpesviruses are not necessary. Currently, there is no practical test system for hepatitis B virus titration. The duck hepatitis B virus (DHBV) may be used as a model of human HBV. However, it requires the use of its natural animal host (duck or primary duck cells) for titration. In consequence, there is no general requirement to include DHBV in the virus panel.

Non-enveloped viruses SV40 and animal parvovirus

Infectious polyomaviruses, adenoviruses and enteroviruses can be found in human urine. SV40 as a member of the polyomaviridae virus family should be used in validation studies. SV40 is also relevant to represent HBV in size exclusion steps. Viruses which can be excreted at high titers in human stool include many non-enveloped DNA or RNA viruses such as adenoviruses, hepatitis A virus (HAV) and other enteroviruses, hepatitis E virus, noroviruses and astroviruses. An appropriate model for highly resistant small non-enveloped viruses should be incorporated in the panel. This may be chosen among porcine, canine, bovine and murine parvoviruses. In some specific cases, it may be justified to include HAV in the panel to model enteroviruses (for example when one step is not expected to be efficient on a more resistant virus like porcine parvovirus).

4.4. Overall viral and TSE safety

Urine-derived medicinal products have been used in the treatment of a number of conditions for several years without any suspicion that they are responsible for the transmission of any infectious agents. It is nevertheless fundamental to perform risk assessments for the overall transmission risks for urine-derived medicinal products.

The following are likely to be the main components of each overall risk analysis. Estimates of the robustness of the analysis in each case might usefully accompany each component.

1. Viral epidemiology for the region where collection takes place, and for the specific donor population there (i.e. on the basis of age, gender, and endocrinal status).
2. On the basis of the epidemiology data and taking into consideration the capacity for human kidneys, urinary and genital tracts to harbour pathogens, agents which are most likely to be relevant for the product could be identified.
3. Donor selection criteria, encompassing donor briefing strategies with an estimate of how effective they might be in particular populations, and donor motivation factors.
4. The donation and collection system up to the start of pooling, and including the security and hygienic measures in place.
5. Any information available on the Quality Assurance System, Audits and Procedures followed by the manufacturers to control the collection system and early production steps of the different manufacturers/suppliers.
6. Pooling strategies with a consideration of screening tests performed.
7. The extraction and purification methodologies, including a consideration of any further pathogen screening tests applied, and the indication of the point at which GMP starts.
8. The effectiveness of each TSE agent and virus elimination step applied and the relevance of the results obtained with model viruses used in validation studies with regards to the virus that may be found in the starting material.

Where practicable, consideration should be given by companies to presenting estimates of the probabilities of individual doses of a urine-derived medicinal product being contaminated with a pathogen. Such risk analyses should follow the methodologies developed for plasma derived medicinal

products and should take into account viral safety aspects described in the plasma derived medicinal products guideline[5] and the guidance concerning reduction of TSE agents discussed in the "CHMP Position statement on Creutzfeldt-Jakob Disease and Plasma-derived and Urine-derived Medicinal products"[3] and in the guideline on "Investigation of Manufacturing Processes for Plasma-derived Medicinal products with regard to vCJD risk".[6] Risk analyses of this nature should appear in 3.2.A.2 Adventitious Agent Safety Evaluation of Marketing Authorisation applications.

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