

7<sup>th</sup> September 2011

**RAPID IMPLEMENTATION OF REVISED MONOGRAPH**  
**HUMAN NORMAL IMMUNOGLOBULIN FOR INTRAVENOUS ADMINISTRATION (0918)**

Please note that *Revised monograph 0918 Human normal immunoglobulin for intravenous administration* to be published in supplement 7.5 has been adopted following a fast-track procedure and is to be implemented on 1 January 2012 (see [Resolution AP-CPH \(11\) 6](#) of the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH) (Partial Agreement)), i.e. the publication date of this supplement. During this fast-track procedure the production section was revised considering the recent experience with an immunoglobulin preparation which caused an increased rate of thromboembolic events and concerns for public health associated with these events. Although the current wording requests the establishment of an impurity profile, the revised paragraph was elaborated to make users of the monograph aware of this particular issue and to request identification and removal of such thrombosis agents. The new wording of the production section reads as follows:

“PRODUCTION

The method of preparation includes a step or steps that have been shown to remove or to inactivate known agents of infection; if substances are used for inactivation of viruses, it shall have been shown that any residues present in the final product have no adverse effects on the patients treated with the immunoglobulin. The method of preparation also includes a step or steps that have been shown to remove thrombosis-generating agents.

Emphasis is given to the identification of activated coagulation factors and their zymogens and process steps that may cause their activation. Consideration is also to be given to other procoagulant agents that could be introduced by the manufacturing process.

The product shall have been shown, by suitable tests in animals and evaluation during clinical trials, to be well tolerated when administered intravenously.

Human normal immunoglobulin for intravenous administration is prepared from pooled material from not fewer than 1000 donors by a method that has been shown to yield a product that:

- does not transmit infection;
- at an immunoglobulin concentration of 50 g/L, contains antibodies for at least 2 of which (1 viral and 1 bacterial) an International Standard or Reference Preparation is available, the concentration of such antibodies being at least 3 times that in the initial pooled material ;
- has a defined distribution of immunoglobulin G subclasses ;
- complies with the test for Fc function of immunoglobulin (2.7.9) ;
- does not exhibit thrombogenic (procoagulant) activity.

Human normal immunoglobulin for intravenous administration is prepared as a stabilised solution or as a freeze-dried preparation. In both cases the preparation is passed through a bacteria-retentive filter. The preparation may subsequently be freeze-dried and the containers closed under vacuum or under an inert gas. No antibiotic is added to the plasma used. No antimicrobial preservative is added either during fractionation or at the stage of the final bulk solution.

The stability of the preparation is demonstrated by suitable tests carried out during development studies.”

Particular attention should be given to the wording “does not exhibit thrombogenic (procoagulant) activity”, introduced in analogy to the statement on infectious agents where the monograph requests that:

“The method of preparation includes a step or steps that have been shown to remove or to inactivate known agents of infection; if substances are used for inactivation of viruses, it shall have been shown that any residues present in the final product have no adverse effects on the patients treated with the immunoglobulin”.....”does not transmit infection”.

The absolute nature of this newly added wording and the comprehension/interpretation that should be made of this statement were discussed within the European Pharmacopoeia Commission and the following consensus was reached:

Although in both cases the target is to have no (zero) infectious/thrombogenic agents, consideration should be given to the limitation of manufacturing processes, detection methods and what is considered as a safe level. From a scientific point of view, ensuring that no viral particles are present or active in every single vial is not achievable due to the inherent limitations of the techniques used. Similarly, presence of potential thrombogenic agent(s) might not be absolutely excluded, however the safety profile of these products might not be impaired by their presence or the level of these agents is not detectable. Moreover, for the time being, the acceptable “safe level” of these thrombogenic agents is unknown and for the sake of public health, with respect to the monograph, a cautious approach was considered aiming at totally excluding their presence. The proposed wording for the thrombogenic agents was selected considering these aspects.

Therefore, manufacturers have to provide sufficient data showing that they achieve a level that can be considered as safe by competent authorities. Assessors have to base their decision on the data presented by manufacturers showing that they achieve and have the capacity to detect a level considered to be safe.

Should a product contain thrombogenic agents, the decision to consider that the safety level demonstrated by the manufacturer is sufficient and sufficiently documented lies within the competent authority.

It was also agreed that the current state of the monograph would be an interim phase until a safe level and a harmonized method(s) could be identified and commonly agreed for the concerned agent(s). Collaborative work is currently ongoing in this field.

In addition, minor editorial improvements were made in the majority of the sections to bring the monograph in line with the recently adopted Technical Guide for elaboration and use of monographs on human plasma.