Viral Safety Perspective from the Paul-Ehrlich-Institut in Europe

Johannes Blümel

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According to European Directive 2001/20/EC, authorization of clinical trials is in the responsibility of national member states (1). In order to facilitate a harmonized evaluation of viral safety issues, a European guideline on viral safety evaluation of biotechnological investigational medicinal products (EMEA/CHMP/BWP/398498/2005) was released in 2008 (2). This guideline defines the basic principles on data requirements for viral safety. It further opens the possibility for proving a reduced data package compared to the requirements for marketing authorization as outlined in guideline ICH Q5A (3).

Effective process steps for viral clearance are considered essential for safety of biological products. The aim is to design steps to clear a wide range of different viruses in order to cover undetected, unexpected, or unknown emerging viral contaminants. According to the guideline, “it is desirable to investigate the contribution of more than one production step for virus reduction and at least two orthogonal steps should be assessed. . .”. Orthogonal steps are defined as unit operation process steps where different mechanisms are responsible for virus inactivation/removal. The criteria for an effective viral clearance step (referred to in this article as viral clearance unit operation) have been outlined in Note for Guidance on Virus Validation Studies (CPMP/BWP/268/95) and include a virus inactivation/removal capacity in the order of 4 log10 (4). In addition, aspects considering the robustness of the process steps and other critical experimental factors during validation have to be considered. In the case of using rodent cells for production, which can produce endogenous retrovirus-like particles in variable amounts, it is necessary in many cases to evaluate more than two process steps (unit operations) in order to demonstrate an adequate safety margin. For well-tested cell cultures where no virus or only endogenous rodent retroviruses have been detected, a reduced panel of only two model viruses is acceptable for evaluation of viral clearance. A retrovirus is used in order to evaluate clearance of endogenous retrovirus or retrovirus-like particles from rodent cell lines.

A stable, small, nonenveloped virus (e.g., parvovirus) has been suggested as a non-specific worst case model, due to its physicochemical resistance and small size. Usually, evaluation experiments have to be performed in duplicate and product-specific process intermediates have to be used to cover potential or unexpected product-specific factors affecting viral clearance. However, in-house data from similar types of products are considered helpful in order to evaluate the influence of process parameters on viral clearance and can reduce the required amount of product-specific studies (e.g., justification for performing single confirmatory product-specific runs).

The Paul-Ehrlich-Institut is actively participating in experimental research projects on virus inactivation and is performing meta-analysis of viral clearance data from many products. In some cases inactivation data from other antibodies have been accepted for low-pH incubation (pH 3.5 with upper limit of 3.6) or detergent-based inactivation after careful analysis of the provided in-house database. Product-intermediate specific data for chromatographic clearance steps and clearance of parvoviruses during virus-retentive filtration are still requested. Retroviruses are usually consistently removed by suitable virus filters below the detection limit. However, the titer of the virus spike seems to limit the reduction factor (log reduction value, LRV), which can be experimentally demonstrated. Considering the much larger size of retroviral particles it seems to be possible to claim an LRV demonstrated with parvoviruses as an LRV also for retroviral clearance. However, this approach might underestimate retrovirus clearance in cases where the clearance of parvoviruses is limited.

References


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Johannes Blümel, Ph.D.
Paul- Ehrlich-Institut; Langen, Federal Institute for Vaccines and Biomedicines, Langen, Federal Republic of Germany
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