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Dear Alexis:

The Parenteral Drug Association (PDA) is pleased to provide these comments on the draft Guideline on Virus Safety Evaluation of Biotechnological Investigational Medicinal Products. PDA is an international professional association consisting of almost 10,000 individual members having an interest in the fields of pharmaceutical manufacturing and quality. Our comments were prepared by an international working group consisting of industry professionals from pharmaceutical companies and service providers.

PDA welcomes guidance in the area of virus safety evaluation for Investigational Medicinal Products (IMPs) and we support efforts for a harmonized approach. Attached, please find specific detailed suggestions regarding the draft guideline. Our general suggestions are summarized below

- Regarding design of virus clearance studies, the worst-case parameters for virus removal are not always understood and should not be assumed to be the worst-case parameters for other performance attributes like step yield or peak resolution.
- It should be made clearer that column lifetime studies are tied to MAA, not Phase III trials.
- In our opinion, provision of raw data should be limited to special situations only, e.g., when a novel technique is used. We would like clarification about when raw data for virus testing and virus validation will be requested for submission (Sections 4.3/4.5).
- Viral safety testing at the end of production should follow a risk-based approach. For example, we are concerned that the document has an implied expectation that (1) cell culture manufacturing processes are set early in development and do not evolve as the products proceed in development or (2) that extensive testing should be required between each production run, if even minor changes are made. Neither of these two scenarios is in alignment with the current practice of clinical product development. In reality, clinical runs of the same product in development can have varying cell culture lengths and concomitant varying cell age (measured as cell doublings). Changes are common because of increasing demand as products traverse phase 1 through 3, because of improvements in the cell cultures strategy that increase productivity, product uniformity and other quality attributes, and because of scale changes. The draft guideline states each time there is an extension of the cell age the limit of in vitro cell age studies must be repeated; in effect multiple studies would need to be

performed for each new product. Successful products can have many production runs during clinical development in order to meet the demands of large clinical trials; each one may have an incrementally increased cell age. These studies can require 4-6 months of testing because the assay panel includes in vivo studies and co-cultivation studies for retroviruses. We feel that this requirement would have the impact of discouraging cell culture process optimization, possibly even negatively impacting product consistency optimized during this development process.

- Application of ICH Q5A, unless justified due to unusual risk, is a burden to industry that could delay Phase III trials. For example, we are concerned about the stated requirement in this draft guideline that viral clearance validation studies conforming to ICH Q5A should be performed prior to the use of investigational products in Phase III clinical studies. In general, full conformance with ICH guidance documents is an expectation for marketed, not investigational, products. We fully agree that viral safety is a very serious concern; this principle should not be compromised. However, the current industry practice for phase III trials does not include full conformance with each aspect outlined in ICH Q5A for virus clearance studies. Instead, industry takes a holistic approach for each investigational product by evaluating all the components of the viral safety program in place (e.g. careful raw material selection and testing, well characterized and tested cell lines, demonstration of robust clearance by the process of enveloped and non-enveloped model viruses, etc). Given the excellent safety record of industry as a whole in assuring the viral safety of investigational biopharmaceutical products, we feel that it is warranted to allow flexibility to conduct the Q5A viral validation studies during phase III clinical development instead, with the requirement to submit full reports later in the marketing authorization application.
- Regarding the testing and validation requirements for phase III products, different sections of the document word EMEA's expectations differently. We provide examples of the different wording in our detailed in the accompanying comments. Please consider unifying the language describing testing and validation expectations in the different sections of the draft.
- Acceptability of in-house data on virus removal by chromatography should be clarified. PDA welcomes the concept of in-house experience in the draft document. We feel that acceptance of in-house virus validation experience will streamline product development and improve product safety. Our one concern is that we feel that in-house data for chromatography steps is probably more robust and reliable than the draft document allows. We feel that manufacturers with extensive experience with virus removal by chromatography can provide examples of this robustness and reliability; we would welcome a more extensive discussion of this issue.

PDA would be pleased to meet with the BWP to discuss our comments, and PDA would also be willing to attend and/or co-sponsor a public meeting to hear and understand the concerns of BWP and to jointly work with BWP on proposed alternative wording. Any questions regarding these suggestions should be addressed to Dr. Richard Levy, Senior Vice President, Scientific and Regulatory Affairs at levy@pda.org.

Thank you again for the opportunity to provide input.

Kind regards

A handwritten signature in black ink, appearing to read 'Georg Roessling', is positioned to the left of a vertical red line. A small yellow square is located at the bottom of the signature.

Georg Roessling, PhD
Senior Vice President, PDA Europe

cc: John Geigert, Co-Chair of PDA Biotechnology Advisory Board
Gail Sofer, GE Healthcare and Co-Chair, PDA Biotechnology Advisory Board
Zena Kaufman, Abbott Laboratories and Chair of PDA RAQC
Richard Levy, Senior Vice President, Scientific and Regulatory Affairs, PDA