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By Electronic Mail

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Emmanuelle Charton, Ph. D.
Deputy Head, European Pharmacopoeia Department
European Directorate for the Quality of Medicines and HealthCare
7, Allée Kastner; CS 30026
F-67081 Strasbourg (France)

Re: Pharmeuropa Vol. 21, No.1, January 2009, proposed revisions to:
Chapter 2.6.16. Test for extraneous agents in biological products, &
Chapter 5.2.3. Cell substrates for the production of biological products

Dear Dr. Charton,

On behalf of PDA, I am writing to request that EDQM temporarily suspend, pending scientific discussion, the revision process for Chapters 2.6.16. and 5.2.3. Our request is based on a review by PDA experts with expertise in this subject matter, and is approved in accordance with PDA's internal governance procedures. As you know, it is PDA practice to focus our comments on scientific and technical issues which affect the utility and value of regulatory standards and requirements.

We note the original scope of both chapters was limited to vaccines for human use. In the proposed revisions, both in title and text, the word "vaccine" has been globally replaced by the term "biological product." This simple change in wording appears to expand the scope of both chapters to include many other biological products, ranging from blood derived materials, to gene and cell therapy products, to recombinant proteins and monoclonal antibodies. The expansion of scope to include such products, without a case by case consideration of the underlying science, technology, regulatory paradigm, and use of the products, is not appropriate and may result in unforeseen and undesirable consequences.

We illustrate our concern with the following examples:

1) Adverse Effect on Marketed Products: The statement in Chapter 5.2.3 (top of page 60) that 'Cell lines that show the presence of retroviruses capable of replication are not acceptable for production of biological products' is problematic in that it would remove from the market, and block approval of, any monoclonal antibody or recombinant protein manufactured in a murine substrate or in a rodent substrate with a positive infectivity assay result. Current purification schemes are sufficiently robust to achieve reductions in retroviral load well in excess of the amounts of retrovirus that may be present in the unpurified bulk material. The restriction may be appropriate for products which undergo limited to no purification, and or for highly purified products manufactured from human or simian substrates in which an infectious retrovirus is elaborated. However, extension of this requirement from vaccines to all biological products is unwarranted.

2) Inconsistency with International Consensus Guidance: The proposed revisions to Chapters 5.2.3 and 2.6.16 are inconsistent with ICH Q5A and with ICH Q5D with respect to testing of the Master Cell Bank for biotechnological products, and with respect to tumorigenicity testing. Also, the current approach for biopharmaceutical viral safety has been established over the last two decades through extensive dialog between industry and the regulatory authorities. Hence,

the resulting approach and guidance for biological products differs substantially from that for vaccines. For example, according to the revised Table 5.2.3-1, testing for extraneous agents in cell culture and in animals and eggs is not required on the production substrate. This statement is contradictory to recommendations in ICH Q5A (see Table 1).

3) Clarity of Regulatory Standard: The change from 'vaccine' to 'biological product' has rendered these chapters open to multiple interpretations due to the application of vaccine-specific terminology and concepts to other product classes. Any attempt to broaden the scope of the chapters should begin by harmonizing with internationally accepted terminology, and then be followed by definition of additional terms that may be required for each product class. Without a common understanding of the terminology used, a uniform interpretation of the standards for product quality cannot be assured.

4) Tests for Extraneous Agents, 2.6.16: To summarize the testing requirements for extraneous agents for a broad range of product classes in one general test method is not practical. Different product classes have different risks, and the approaches taken to minimize these risks differ significantly. In the case of viral vaccines, it is difficult to test for extraneous agents in the presence of the vaccine agent, as reflected in the original version of Chapter 2.6.16. The framework for assuring the safety of vaccines differs from that for other biological products because the manufacturing process provides only limited capacity for removal or inactivation of viral contaminants. However for many other products such as rDNA products or plasma derivatives, effective extraneous agent removal can be included in the production processes. In summary, it seems impractical to summarize the tests for extraneous agents in biological products with one method of analysis.

In summary, we believe that the proposed expansion of the scope of Chapters 5.2.3 and 2.6.16 from vaccines to all biological products will have a number of negative, unintended consequences for the other biological products. The resulting changes are not scientifically sound nor do they represent appropriate medicinal standards. If adopted, these changes may lead to:

- Increased costs without benefit to patients.
- Reduced availability of currently marketed biopharmaceuticals, and potentially new biological products, due to unnecessary and, in some instances, scientifically impractical test standards.
- Conflict with accepted ICH guidelines, well accepted industry standards and other standards within *Ph.Eur.*

Therefore, PDA requests that EDQM temporarily suspend the revision process for these chapters pending scientific discussions regarding the technical and economic impact of the changes on affected products and on patient care. PDA can assist with the process should EDQM desire support. Thank you again for the opportunity to support your activities. Please contact me, or James Lyda (lyda@pda.org) of my staff, if you have any questions.

Very best regards,

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cc: RAQC, BioAB, Biotech Interest Group

Enclosure