For virus safety evaluation of biotechnology products during phase 1–3 clinical development, no regulatory guidance currently exists for the ICH regions European Union, Japan, and the United States. (Biotechnology products in this article refers to those prepared from cells cultivated in vitro from cell banks of human or animal origin, with the exception of microbial metabolites such as antibiotics, amino acids, carbohydrates, and other low molecular weight substances — the definition given in Guideline ICH Q5D.) ICH Q5A, Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin, is clearly limited in scope: “This document . . . outlines data that should be submitted in the marketing application/registration package” (1).

The only available document providing viral-safety guidance is the FDA's Points To Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (PTC), published in 1997 (2). It applies the basic concepts of the ICH Q5A guideline and describes the possibility for a modified virus safety evaluation of monoclonal antibodies (MAbs) that are intended to be administered in clinical studies of serious or immediately life-threatening conditions. It also outlines the option for a sponsor to make use of “generic” or “modular” virus clearance studies if the sponsor wants to move a series of MAbs into clinical development. Although the PTC document focuses on only one specific group of biotechnology products, it currently is the only document for sponsors to consult when evaluating the viral safety of their products in development.

The Changing Regulatory Environment

Until May 2004, no further guidance on virus safety was developed in the ICH regions, although many biotechnology products were under development and subsequently approved in those regions. However, the regulatory environment changed with implementation of the EU Clinical Trials Directive 2001/20/EC (3). All EU Member States now require submission of an Investigational Medicinal Product Dossier (IMPD) (an equivalent of the US IND) starting at phase 1. The virus safety evaluation for biotech products is part of the IMPD’s quality documentation (in addition to clinical, preclinical, and other quality documentation) (3).

The EU Clinical Trial Authorisation (CTA) application is to be submitted for the EU Member State in which a sponsor intends to run the study. This setup is different from, for example, that of the US IND process, which leads to a centralized approval of a clinical study. Therefore, guidance on virus safety in development becomes a desirable instrument to guarantee a harmonized assessment by the different Member State authorities, e.g., to prevent different opinions in the context of multicentric studies.

A Concept Paper: The EMEA Biologics Working Party (BWP) decided to develop guidance on virus safety in its 2004–2005 work program. The BWP published a concept paper concerning development of that guidance in late 2004 (4). Below is a short overview of this Concept Paper:

- The future guideline intends to address biotechnology products only;
- All phases of clinical development will be covered;
- Manufacturers may be able to make reference to so-called “in-house experience” concerning virus safety evaluation: “Such a database may serve as supportive data to justify a reduced virus safety evaluation program for new products that enter development. Depending on the content of the database the
requirements for performing product specific virus safety studies may thus vary” (4). The elements of such a database are not listed specifically in the Concept Paper, but they can be implied from the list provided: “The criteria to take into consideration in the design of preliminary viral safety evaluation studies include:

- the nature of the cell line
- the history and use of the cell line
- use or non-use of raw materials of human and/or animal origin
- exposure to adventitious contamination
- prior data on viral inactivation and/or removal steps
- experience of the company with the cell line involved
- experience of the company with specific inactivation/removal procedures to be used
- published data.”

The future guideline will also define “the risk analysis which should form part of the safety evaluation, and the level of requirements with respect to the stage of development and the format of data to be presented.”

In summary, the concept paper aims to set up a guideline allowing sponsors to use in–house virus safety data to justify their virus safety programs for biotechnology products scheduled to enter clinical studies. This concept appears valid, taking into consideration the safety record of the many approved biotechnology products — especially MAbs — for which the same well-characterized cell lines and almost identical manufacturing processes are used.

**STATUS**

The Concept Paper was commented upon by EFPIA (the European Federation of the Pharmaceutical Industry Associations) in March 2005. The intention to develop a guideline for virus safety was welcomed, and a joint working group of EU regulators and industry representatives was proposed.

In the spirit of that proposal, industry drafted a guideline based on the Concept Paper for further discussion (an overview of that draft guideline is provided below). The draft intentionally follows the structure of ICH Q5A and further develops the proposals of the BWP Concept Paper. According to information from the EMEA, a first draft of the BWP guideline may be expected in late autumn of 2005.

**Overview of the Draft Industry Guideline**

**Adequate safety for the clinical trial subjects is of paramount importance in virus safety studies for biotechnology products. A virus safety risk assessment evaluates the production cell line as well as the virus clearance capacity of the production process in relation to the indication, the dose, the frequency of administration, the number of patients exposed, and the study duration.**

For early development (defined as phase 1/proof–of concept type clinical studies and phase 2–type studies such as dose finding studies), in–house experience as well as published data may be used for performing the risk assessment. For late-stage development, each assessment should put emphasis on product–specific virus validation data, but with support from in–house experience and published data. Whether a sponsor can sufficiently justify reduced testing will therefore depend on the content of the in–house database:

- Cell line testing should be performed as described in ICH Q5A, independent of the development stage. In–house experience may be used to justify reduced testing. For example, a Master Cell Bank (MCB) could be generated in a facility dedicated to the generation of cell banks, with minimal potential contact to adventitious agents, and the viral safety of this step could be demonstrated using previous MCBs.
- Unprocessed bulk testing should be performed as described in ICH Q5A, independent of the stage of development.
- Concerning virus clearance procedures in early development, and if well–defined cell lines are used for production, virus validation studies with at least one relevant virus (e.g., a model virus for an endogenous retrovirus present in the cell line) are usually sufficient, provided that at least two orthogonal, robust virus clearance steps are implemented in downstream processing (e.g., nanofiltration and a low pH step).
- For late development products (phase 3-type studies), full validation according to ICH Q5A should be initiated if the final production and purification process has been established.

**SUMMARY**

The need for guidance on virus safety in the development of biotechnology products was triggered by new EU legislation on clinical trial authorization. EU regulators have recognized the need for a harmonized assessment of the safety of such products to enable multicentric studies in the European Union. The EU pharmaceutical industry agreed that guidance is needed and has provided a draft guidance in ICH Q5A format that could serve as a starting point for discussion among the experts. In particular, the elements and detail required for an “in–house experience” database that might justify a reduced virus safety evaluation will be a main focal point of the guidance: This database will determine the virus safety program for new products entering development that are planned to undergo clinical studies in the European Union.

**REFERENCES**


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