

EMA issues new guideline on virus safety evaluation of biotechnological investigational medicinal products

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The risk of virus contamination is a feature common to all biotechnology products produced from animal or human sources. Contamination can arise from a source cell line or from adventitious virus introduced during production. The approach to ensuring viral safety includes several complementary approaches, which are laid out in guidelines from the FDA, EMA and ICH (references 1-4). These guidelines address the viral safety testing requirements for applications for marketing authorization. A guidance document recently issued by the EMA (reference 5) provides regulatory guidance specifically for investigational medicinal products (IMP) for use in clinical trials.

In large part, this guidance captures current practices acceptable to the regulatory agencies, but there are a few new recommendations. Here are some of the testing recommendations contained in this new guidance.

Scope

This guidance envisions a reduced level of virus safety testing for IMP as compared to the testing required for marketing authorization. The reduced program applies only to monoclonal antibodies and recombinant DNA derived IMP that are produced in cell lines where no virus (or virus-like particles) other than retrovirus has been demonstrated in the cell banks or unprocessed bulk. This guidance does not apply to products containing recombinant viruses or bacteria, to live attenuated or inactivated vaccines, or to hybridoma cells grown *in vivo*.



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Risk assessment

Testing should be based on a risk assessment that takes into account a number of factors, including the source, history and characterization of the cell line, use of animal or human-derived materials during production, and the potential for adventitious virus exposure. The risk assessment should be reviewed if process changes that could affect virus safety are made during development of the IMP.

Cell line qualification

Testing of the Master and Working Cell Banks should be performed as specified in ICH Q5A (reference 4) prior to initiation of a Phase I clinical trial. Testing of cells at the limit of *in vitro* cell age is not required as long as testing of the unprocessed bulk is performed.

Raw materials of biological origin

A risk-based assessment should be carried out, focusing on the type and origin of the material, process conditions and testing, its use in the manufacture and on testing of the unprocessed bulk. No specific testing is required.

Unprocessed bulk

Each batch of unprocessed bulk material should be tested as specified in ICH Q5A. Test samples should include cells where appropriate. Testing should include *in vitro* and PCR-based assays as applicable for screening for adventitious viruses and retroviral particles. No further testing is necessary for products produced in CHO cell lines. For products produced in NSO or SP2/O cell lines, tests for infectious retroviruses should be performed once. For other cell lines, tests for infectious retrovirus and *in vivo* tests should be performed once. If there is a significant change in the cell production, these tests should be performed again. Testing for MMV should be considered if the cell line is permissive for this virus. Additional testing may be required if human or animal derived raw materials are used (e.g., bovine serum).



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- Bovine & Porcine Viral Screens
- Infectivity Assays

Virus clearance studies

As always, these studies are evaluated on a case-by-case basis. Virus clearance studies must be performed prior to entering clinical trials and should follow the principles of ICH Q5A. Studies should be performed using worst-case parameters; however, if these have not been established, representative conditions may be used if the manufacturing process was actually run at these conditions. At least 2 viruses should be used, one enveloped virus and one non-enveloped virus (preferably a parvovirus). At least 2 orthogonal production steps should be evaluated. The reproducibility of an effective step should be assessed by performing at least two independent experiments. If changes are made in the manufacturing process, a re-evaluation of the virus clearance results may be needed.

Reduction in virus clearance requirements

A single virus clearance step might be sufficient if the step is demonstrated to be effective for clearance of a broad range of viruses, but a single step would probably not be sufficient for products made in a cell line that carries retrovirus. If a manufacturer has prior experience

using a specific processing step with a similar product under the same conditions, prior results may be applicable to the new product. However, the manufacturer must have thoroughly studied the parameters that affect virus reduction. If data is available from more than one product, the results must be comparable. Upstream processing steps should also be similar between the new and the established product. If the rationale for use of prior data is not entirely convincing, at least a single run with an appropriate virus should be performed to confirm that the step performs as expected. Column re-use studies do not need to be considered unless the column is extensively re-used during manufacture of the IMP.

Impact of new guideline

What is the impact of this new guidance, as compared to the testing strategies in current use for IMP? That will depend on the circumstances. For example, manufacturers using a platform approach for purification of several similar products may be able to perform more limited viral clearance studies. However, in other cases the extent of viral clearance studies may be increased due to the requirement for duplicate runs. Although this guideline

sets a stricter testing standard for IMP than currently required by the FDA, many manufacturers will likely follow them so that they can perform clinical trials in Europe as well as the US.

References

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