DECISION

No. 18/27.11.2009

on the approval of the Guideline on the viral safety evaluation of biotechnological investigational medicinal products

The Scientific Council of the National Medicines Agency,
set up based on Minister of Public Health Order No. 1027/22.05.2008, as amended, reunited on summons of the National Medicines Agency President in the ordinary meeting of 27.11.2009, in accord with Article 10 of Government Ordinance no. 125/1998 related to the set up, organisation and functioning of the National Medicines Agency, approved as amended through Law No. 594/2002, as further amended, agrees on the following

DECISION

Single article. – The Guideline on the viral safety evaluation of biotechnological medicinal products, in accordance with the Annex which is integral part of this Decision.

PRESIDENT
of the Scientific Council
of the National Medicines Agency

Acad. Prof. Dr. Victor Voicu

ANNEX

Guideline

on the viral safety evaluation of biotechnological investigational medicinal products

CHAPTER I

Introduction and legal basis

Art. 1. – This Guideline is a translation into Romanian and an adaptation of the *Guideline on virus safety evaluation of biotechnological investigational medicinal products* (EMEA/CHMP/BWP/398498/2005).

Art. 2. - Assuring the viral safety of biotechnological medicinal products is a complex process and a reliable assessment of the viral safety of an investigational medicinal product (IMP) is critical.

Art. 3. - (1) This guideline provides advice on the viral safety data and documentation that should be submitted in a request for authorisation of a clinical trial of a human biotechnological medicinal product.

(2) Reference is made to ICH Q5A (ICH Q5A: Harmonised Tripartite Guideline on the safety evaluation of biotechnological medicinal products obtained via human/animal cell lines), which defines data requirements for marketing authorisation applications.

(3) Although Q5A does not provide specific guidance for biotechnological products in clinical development, the basic principles remain pertinent and applicable.

Art. 4. - (1) The guideline provides for a harmonised approach throughout the European Union for both sponsors and regulators with regard to assessment of viral safety of biotechnological IMPs during clinical development.

(2) This will be especially beneficial for multi-centre studies, potentially involving several different EU member states.

Art. 5. - (1) Clinical trials within the EU are regulated by Directive 2001/20/EC, transposed into Romanian by Minister of Health Order No. 904/25 July 2006) and investigational medicinal products used in trials should be manufactured according to the principles of Good Manufacturing Practice.

(2) Approval of trials is the responsibility of individual member states and of the National Medicines Agency, which are required to evaluate the products used in clinical studies.

CHAPTER II

Purpose

Art. 6. - (1) The purpose of this document is to provide scientific recommendations concerning the viral safety of biotechnological medicinal products used in clinical trials.

(2) Provided recommendations refer to:

a) The criteria and magnitude of the assessment studies of viral safety, required before and during clinical development.

b) The extent to which manufacturers are able to refer to their internal experience concerning the assessment of viral safety.

c) Risk assessment, which should be included in the viral safety assessment.

CHAPTER III

Scope

Art. 7. - (1) This guideline applies to human biotechnological IMPs prepared from cells cultivated *in vitro* from characterised cell banks of human or animal origin in accordance with the provisions of Q5A.

(2) Several investigational medicinal products are derived from well-known and well-characterised rodent cell lines such as CHO, NS0 or SP2/0.

(3) However, other cell lines are currently employed and under development and should be trated on a case-by-case basis.

Art. 8. - (1) The Guideline refers to investigational medicinal products such as monoclonal antibodies and recombinant DNA-derived products, including vaccines which contain recombinant subunits.

(2) The guideline does not apply to investigational medicinal products which contain recombinant viruses or bacteria (replicative/non-replicative) or live attenuated/inactive vaccines.

(3) Investigational medicinal products derived from in vitro hybrid cells are also excluded from this guideline's scope.

Art. 9. - (1) This guideline emphasizes the viral safety requirements applicable throughout all clinical development stages of investigational medicinal products.

(2) This Guideline does not apply to investigational medicinal products used only in non-clinical trials.

(3) ICH Q5A provides recommendations concerning the documentation required in view of obtaining a marketing authorisation.

CHAPTER IV
Provisions

IV.1 General principles

Art. 10. - The aim of virus safety studies for biotechnological IMPs is to demonstrate an acceptable level of safety for clinical trial subjects.

Art. 11. - The viral safety of a licensed biotechnological medicinal product is assured by three complementary approaches involving:

(i) selecting and testing cell lines and other raw materials of human or animal origin for viral contaminants,

(ii) assessment of the capacity of downstream processing to clear infectious viruses,

(iii) Testing the medicinal product at appropriate steps for contaminating viruses (Harmonised Tripartite Guideline on the safety evaluation of biotechnological medicinal products obtained via human/animal cell lines).

Art. 12. - (1) For biotechnological IMPs, due to the developmental nature of the manufacturing process and of the medicinal product, a reduced programme of studies on assuring viral safety is envisaged compared with the data requirements for marketing authorisation; firstly, for testing for viruses in end of production cells/unprocessed bulk (see Section 4.2.3) and secondly, for studies on the validation of virus reduction (see Section 4.2.4).

(2) Such a reduced programme would only be applicable for cell lines classified in ICH Q5A as 'Case A' or 'Case B'.

(3) Demonstrated in-house experience (see Section 4.2.4) could also contribute to a reduced package of studies on virus reduction.

Art. 13. - In addition to the provision of data, a risk assessment should be made taking into account some or all of the following factors:

- the nature and history of the cell line,

- the extent of characterisation of the cell line,
- use of raw materials of human and/or animal origin during manufacture and their control,
- potential for product exposure to adventitious contamination,
- experience of the manufacturer with the cell line involved,
- experience of the manufacturer with specific virus reduction procedures to be used,
- published data.

IV.2 Assuring the viral safety of biotechnological IMPs

IV.2.1 Cell line qualification: testing for viruses

Art. 14. - Testing of the master cell bank (MCB) for viral contaminants should be performed as described in Q5A prior to the initiation of a Phase I trial.

Art. 15. - A working cell bank (WCB) might only be set up during clinical development and thus, for some biotechnological IMPs being used early in clinical development, it may not yet have been established.

Art. 16. – (1) When established, the first WCB should in principle be tested as outlined in ICH Q5A.

(2) However, where unprocessed bulks are tested as described in Section 4.2.3/Table 1, testing of cells at the limit of *in vitro* cell age is not required.

IV.2.2 Raw materials of biological origin

Art. 17. – (1) The viral safety evaluation of biotechnological IMPs should take into account biological raw materials (especially animal or human derived) used in production.

(2) A risk-based assessment focusing on the type and origin of the raw material, its process conditions and testing, as well as its use in the manufacture of the medicinal product and tests applied to the unprocessed bulk material, is an acceptable approach to the evaluation of its viral safety (see also Section 4.2.3).

Art. 18. – (1) Appropriate documentation should be provided regarding the viral safety of raw material of biological origin.

(2) Reference is made to guidance documents on bovine sera as well as on minimising the risk for transmission of animal spongiform encephalopathy: Minister of Public Health Order No. 1201/2006 – Guideline on the risk minimisation of animal spongiform encephalopathy agents transmission through medicinal products for human use and CHMP Guideline on the use of bovine serum in the manufacture of human biological medicinal products (CPMP/BWP/1793/02).

IV.2.3. Testing for viruses in unprocessed bulk

Art. 19. – (1) Regardless of the stage of development, each batch of unprocessed bulk material that will be used to manufacture clinical trial material should be tested as per Q5A.

(2) The sample to be tested should include cells, when appropriate, and tests should include *in vitro* and PCR-based screening tests for adventitious agents and an estimation of retroviral particles, where applicable.

(3) No further testing is required for bulks deriving from CHO cell lines.

(4) For manufacture based upon NS0 or Sp2/0 cell lines, tests for infectious retroviruses should be applied on a one-off basis but should be repeated if there is a significant change in production cell culture, e.g. manufacturing scale.

(5) For manufacture based upon any other cell line, tests for infectious retroviruses and *in vivo* tests (as per section 3.2.3 of ICH Q5A) should be applied on a one-off basis, but

should be repeated if there is a significant change in production cell culture, e.g. manufacturing scale.

(6) These testing recommendations are shown in Table 1.

(7) Consideration should be given to the inclusion of a test for MMV (Mouse minute virus) if the cell line is permissive for this virus.

Art. 20. – (1) The source and viral safety of the raw materials used during cell culture should be taken into account when devising the unprocessed bulk testing (see also Section 4.2.2).

(2) Additional specific tests may be required if human or animal derived raw materials are used, e.g. bovine serum.

Table 1 Testing requirements for unprocessed bulks

	***In vitro* testing**	**Tests for infectious retroviruses***	***In vivo**** **testing**
CHO	Yes, for all bulks†	No	No
NSO and SP2/0	Yes, for all bulks†	Yes, once for given scale	No
All other cell lines	Yes, for all bulks†	**Yes, once for given scale**	**Yes, once for given scale**

*****Where possible, test material should contain cells or cellular fragments in order to detect cellassociated viruses. For perfusion cell cultures, manufacturers should determine and justify the most appropriate stage at which to derive samples containing cells for testing.

† Quantification of retroviruses or retroviral-like particles need only be performed for the first three bulks for a specific stage of development (or less, if less than three bulks are prepared).

It is also acceptable to derive test material from cells that have been cultured beyond the scale used to generate the batch of product; in these circumstances, the approach taken should be justified.

Testing for infectious retroviruses may be omitted when more sensitive tests have shown negative results.

IV.2.4 Validation of virus reduction

Art. 21. – (1) The objective of the validation is two-fold; firstly, to characterise and evaluate process steps that can be considered to be effective in inactivating/removing viruses and secondly, to estimate quantitatively the overall level of reduction of any virus/viral particle, e.g. endogenous retroviral particles.

(2) A case-by-case approach will be required taking into account the characterisation of the cell line, the use of raw materials of biological origin, as well as the nature of the process steps that may be effective in inactivating/removing viruses.

Art. 22. – (1) Regardless of the extent of direct virus testing of the production cell line, due to limitations in viral detection assays, there remains a potential for unknown contamination of the cells with a virus originally present in the cells or arising from materials of biological origin that are used during cultivation of the production cells.

(2) Consequently, even when no raw materials of biological origin have been used and the cell line is fully tested, the downstream process for all IMPs should be evaluated for virus inactivation/removal.

Art. 23. - (1) Validation of virus reduction should be performed prior to the onset of the clinical trial.

(2) Potential contaminants may be enveloped or non-enveloped viruses and virus reduction studies should include both an enveloped virus and a small non-enveloped virus, preferably a parvovirus.

(3) It must be demonstrated that any virus or viral particle known to be present in the bulk harvest has been effectively inactivated or removed during downstream processing.

(4) Case B cells (as defined in Q5A) contain endogenous retroviruses or retrovirus-like particles and a retrovirus should be used in validating the inactivation/removal of viruses to demonstrate full clearance of particles present in the bulk harvest.

Art. 24. – (1) Virus reduction studies should be performed according to the principles of Q5A although a demonstration of robustness (i.e. influence of process parameters on virus reduction) may not always be warranted as outlined below.

(2) The relevant steps in product purification that contribute to virus reduction should be described.

(3) The relevant steps in product purification that contribute to virus reduction should be described. The capacity of these steps to inactivate/remove potential virus contaminants should take into consideration the viral safety of the production cell line, e.g. the type and level of endogenous retroviral contamination, or the use of human or animal derived materials during manufacture and possible levels of contamination.

(4) The CHMP Note for Guidance on Virus Validation Studies:The Design, Contribution and Interpretation of Studies validating the Inactivation and Removal of Viruses (CPMP/BWP/268/95) also provides useful detailed information on such studies.

Art. 25. – (1) 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.

(2) Orthogonal steps are defined as process steps where different mechanisms are responsible for virus inactivation/removal.

(3) The criteria for an effective step have been outlined in Note for Guidance on Virus Validation Studies (CPMP/BWP/268/95).

(4) It is not necessary to investigate process steps where no significant virus reduction can be expected.

Art. 26. - The reproducibility of an effective virus reduction step should be demonstrated by at least two independent experiments.

Art. 27. – (1) In performing the validation study, the limits of (i.e. worst-case) process parameters should be used, whenever such conditions are known.

(2) However, during development, such worse case limits may not have been defined for a new manufacturing process.

(3) In these cases, use of representative (i.e. setpoint) conditions is justified as long as the manufacturer can demonstrate that the actual manufacturing process ran at these set-points.

Art. 28. – (1) *Conditions supporting the minimisation of the aforementioned studies:*

a) Investigation of a single specific inactivation/removal step might be sufficient whenever effective virus reduction of a broad range of viruses, including small non-enveloped viruses such as parvoviruses, can be demonstrated for such a step. However, for

case B cells, it will usually be necessary to evaluate more than one step in order to demonstrate adequate clearance of retroviral particles.

b) Experienţa anterioară a fabricantului într-o etapă specifică de prelucrare. În cazul în care fabricantul dezvoltă tipuri similare de medicamente, prin proceduri stabilite şi bine caracterizate, datele de reducere virală derivate pentru aceste medicamente pot fi aplicate la noul medicament la o etapă echivalentă de prelucrare.

The manufacturer's prior experience in a specific manufacturing stage.

In case the manufacturer develops similar types of products, through established and thoroughly enforced procedures, viral reduction data derived for these products may be applicable for the new medicinal product in an equivalent manufacturing stage.

In general, in order to make use of data from such a step, the step should have been carefully evaluated, including a thorough study of the process parameters that affect virus reduction. If data for more than one product is available for the specific step, the effectiveness of virus reduction should be comparable in each case. Processing prior to the specific step for the new and the established product(s) should follow a similar strategy.

A rationale should be provided why prior in-house data can be applied to the new product, e.g. referring to viral reduction data of a particular process step would be possible when the product intermediate at the stage before such a step has comparable biochemical properties and is purified by identical methods. The manufacturer should provide a critical analysis of the manufacturing step for which in-house data will be applied and on the composition of the respective intermediate product.

This should include, for example, the type of filter, load per filter area, flow rates, pressure and composition of product intermediates for virus retention filters, or the column dimensions including bed height, load, composition of buffer and product intermediates, and linear flow rates for chromatographic methods. The analysis should provide complete confidence in the conclusion that in both cases the established manufacturing step is similar in its capacity to inactivate/remove potential virus contaminants.

If the comparison of the step is not entirely convincing, or if the database is not convincing enough to rule out a product-specific effect on virus reduction capacity, at least a single run with an appropriate virus is needed to confirm that the step is indeed performing as expected. If the process performance is clearly different, e.g. different chromatographic profiles are obtained using the same equipment, then the step should be validated as above and according to the principles of Q5A.

(2) Published data can be useful in indicating the potential of a step to inactivate/remove viruses and can provide an insight to the mechanisms involved.

(3) This facilitates an exploration of the key process parameters that affect virus reduction and in setting worst-case limits for specific steps to be validated.

(4) Nevertheless, the application of published reduction factors to a specific product would require extensive demonstration of comparability of the processes involved, of the product intermediates, and an assurance that product specific process factors do not affect virus reduction.

(5) Virus reduction may depend on various process parameters and from the specific composition of a product intermediate.

(6) Furthermore, the assigned reduction capacity may be specific for selected viruses (e.g. chromatographic methods).

(7) Therefore, published data have to be carefully assessed.

(8) Due to the use of dedicated columns and the small number of batches manufactured during early stage development, specific column re-use and sanitisation studies are generally not required for IMPs.

(9) However, whenever columns are extensively re-used for production of IMPs, this should be considered in the investigation of the virus reduction capacity.

Art. 29. – *Revalidation of virus reduction*

(1) The data generated for IMPs used in a previous trial (e.g. a first phase I trial) may be used for subsequent trials.

(2) However, significant changes in manufacture might have been implemented during development of an IMP and it has to be considered that such changes may influence directly or indirectly (by changes other than in the evaluated process steps) the capacity for virus reduction.

(3) Therefore re-evaluation before the start of the next clinical trial will be necessary whenever the available data do not reflect production of the IMP to be used in the forthcoming clinical trial.

(4) Depending on the introduced changes, the selection of viruses should be reconsidered and additional viruses used if needed, to provide confidence in the virus reduction capacity of the process.

(5) Even if a complete validation according to Guideline Q5A is not required in extended clinical trials at late stages (e.g. phase III), manufacturers should justify the approach taken considering the selection of model viruses and evaluated process steps.

(6) Full viral validation studies according to Q5A should be undertaken as soon as the final production and purification process has been established.

IV.2.5 Description and Qualification of Analytical Procedures

Art. 30. – **(**1**)** Different types of analytical procedures can be used to test for viruses in the starting materials and intermediate products, or in assessing the virus reduction capacity of the manufacturing process.

(2) Virus detection assays include broad screen *in vitro* tests evaluating both cytopathic effect (cpe) and hemadsorption in multiple indicator cell lines, *in vivo* tests and specific viral testing using for example PCR.

(3) To test for retroviruses, transmission electron microscopy (TEM), co-cultivation assays using different cell lines and assays for RTase such as Product Enhanced Reverse Transcriptase (PERT) may be used.

Art. 31. – (1) Irrespective of the clinical trial phase, the suitability of the analytical methods used for viral testing, either as a qualitative or a quantitative method, should be substantiated.

(2) Basically, ICH Q5A Chapter 3.2 "Recommended Viral Detection and Identification Assays" and Chapter 4 "Testing for Viruses in Unprocessed Bulk" are applicable.

(3) A sufficiently detailed description of the analytical procedures should be provided, including reagents, assay controls, test procedure, and validity criteria, to allow for a clear understanding of the assay used and how it is controlled.

(4) Where compendial procedures are used, clear references should be given.

Art. 32. – (1) For analytical procedures supporting the qualification of the cell bank system and other starting materials as well as testing of unprocessed bulk for viruses, a tabulated summary of the analytical qualification/validation results of these procedures

should be provided, as appropriate (e.g. results of values found for specificity using appropriate positive and negative controls, sensitivity, quantification and detection limit).

(2) It is not necessary to provide a full qualification report for each method; however such reports should be held available and submitted upon request.

Art. 33 – (1) For analytical procedures supporting the viral reduction studies, full details should be provided which show the suitability of these procedures to quantify the (model) virus particles.

(2) These should include studies to assess, for example, quantification limit, specificity, intrinsic assay variability, buffer/matrix interference with viral infectivity, and product and buffer cytotoxicity that might affect the ability of the selected model viruses to infect the indicator cells.

(3) Statistical considerations for assessing virus assays can be found in ICH Q5A Appendix 3.

(4) Where applicable, a report from a contract laboratory which conducted the viral testing may be acceptable.

IV.3 Virus safety risk assessment

Art. 34 – (1) In addition to the derivation and provision of data on the viral safety of the medicinal product, a virus safety risk assessment should be provided with an application for clinical trial authorisation.

(2) The factors noted under Sections 4.1, 4.2.1, 4.2.2, 4.2.3 and 4.2.4 should be taken into account as the primary factors.

(3) In accordance with Q5A, testing of the cell line and of all raw materials of human or animal origin for viral contaminants, validation of virus reduction and testing of the medicinal product at appropriate steps of the manufacturing process for absence of contaminating infectious viruses should be considered.

Art. 35. - The risk assessment should include the calculation of estimated particles per dose (see ICH Q5A, Appendix 5) and encompass all steps of the production process.

Art. 36. – (1) In particular cases it may be reasonable to consider clinical parameters such as the indication, the dose, the frequency of administration, the number of people exposed, the study duration and the immunological status of the patients in the overall risk assessment for a clinical trial.

(2) In this context, it should be considered that several of these parameters might change between Phases I, II and III.

(3) The clinical parameters should not be considered as primary decision parameters, but they can contribute to the final decision on whether to authorise a clinical trial from the viral safety point of view.

Art. 37. - Each situation will be considered on a case-by-case basis.

IV.4 Re-evaluation of viral safety during development

Art. 38. – (1) Process changes are often introduced during development of an IMP and some of them could impact on a previously determined viral safety assessment.

(2) Whenever changes are introduced in the production process of an IMP for which a viral safety risk assessment has been performed, the manufacturer should document all changes introduced and for each of them should consider if a reassessment of the risk is required.

(3) In some cases it will be clear that the change has no impact on the viral safety risk assessment.

(4) However where there is a clear impact or the outcome is uncertain, the risk assessment should be re-evaluated and where necessary appropriate practical studies performed.

(5) All aspects of viral safety assurance should be taken into account in these considerations.

Art. 39. - For changes that might compromise the validity of virus reduction studies, see paragraph 'Revalidation' in Section 4.2.4.2

IV.5 Format of clinical trial autorisation documentation

Art. 40. - The overall programme of assuring viral safety should be carefully and clearly presented, with explicit justification for any deviation from the minimum recommendations made in this guideline.

Art. 41. – (1) In accordance with SCD No. 49/2006 – *"Guideline for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authority, notification of substantial amendments and declaration of the end of the clinical trial in Romania"* includes a specific attachment, i.e., Attachment 2: 2.1.A Appendices, 2.1.A.2, Adventitious Agents Safety Evaluation, dedicated to the data on TSE agents, virus safety of biotechnological IMPs and other adventitious agents.

(2) All the data should be brought together in this Annex in order to be self-standing and understood in its entirety with minimum references to the other sections of the main dossier.

(3) Full reports including raw data of cell line testing and viral reduction studies should be available upon request.

(4) During evaluation of the submitted data, it may be necessary to request such reports to ensure as clear an understanding as possible of the viral safety of an IMP.

(5) Raw data might be provided by contract laboratories or internal labs as part of the reports.

(6) When the applicant makes use of prior in-house data (i.e. data from other medicinal products), an adequate package of data should be provided to allow an assessment of the inhouse data and to provide confidence that these data are valid or supportive for the specific product under development.

(7) For general consideration on virus safety documentation, information to be submitted can take into consideration the items stated in volume 2B of the Notice to Applicants, Part II V: v*irological documentation*.