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GUIDELINE ON VIRUS SAFETY EVALUATION OF BIOTECHNOLOGICAL INVESTIGATIONAL MEDICINAL PRODUCTS

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GUIDELINE ON VIRUS SAFETY EVALUATION OF BIOTECHNOLOGICAL INVESTIGATIONAL MEDICINAL PRODUCTS

TABLE OF CONTENTS

EXECUTIVE SUMMARY

The purpose of this document is to provide scientific guidance relating to the viral safety of biotechnological medicinal products used in clinical trials. Guidance is provided with respect to:

(i) the criteria for and the extent of viral safety evaluation studies, especially validation studies, that are required prior to and during clinical development.

(ii) the extent to which manufacturers are able to refer to in-house experience concerning virus safety evaluation.

(iii) the risk assessment which should form part of the safety evaluation.

1. INTRODUCTION (background)

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. Reference is made to ICH Q5A (see references), which defines data requirements for marketing authorisation applications. Although Q5A does not provide specific guidance for biotechnological products in clinical development, the basic principles remain pertinent and applicable.

Clinical trials within the EU are regulated by Directive 2001/20/EC (see references) and materials used in trials should be manufactured according to the principles of Good Manufacturing Practice.

Approval of trials is the responsibility of individual member states, which are required to evaluate the products used in clinical studies. 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.

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

2. SCOPE

This guideline applies to human biotechnological IMPs prepared from cells cultivated *in vitro* from characterised cell banks of human or animal origin as described in Q5A. A variety of cell lines are in use or under development although many products are derived from well-known and well-characterised rodent cell lines such as CHO, NS0 or SP2/0.

Thus, the guideline covers monoclonal antibodies and recombinant DNA derived products including recombinant subunit vaccines, but does not apply to products that contain recombinant viruses such as vaccines or gene therapy products using viral vectors. Products derived from hybridoma cells grown *in vivo* are also excluded from the scope of this guideline.

Viral safety requirements for all clinical development phases, from the first clinical studies in humans up to pivotal clinical trials, are addressed. However, it will be clear that the bulk of the guidance provided for validation studies is directed towards materials for phase I and II studies since for phase III materials, validation studies should be performed essentially as described by ICH Q5A (see section 4). The guideline does not apply to material to be used solely for non-clinical testing and guidance is not provided on data required to support a marketing authorisation application (MAA), since this is dealt with elsewhere (viz., ICH Q5A).

3. LEGAL BASIS

Clinical trials within the European Union are regulated by Directive 2001/20/EC. Approval of trials is the responsibility of individual Member States, who are required to evaluate the products used in clinical studies.

4. MAIN GUIDELINE TEXT

4.1 General Principles

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

The viral safety of a licensed biotechnological medicinal product is assured by three complementary approaches involving (i) thorough testing of the cell line and of all raw materials for viral contaminants, (ii) assessment of the capacity of downstream processing to clear infectious viruses and (iii) testing the product at appropriate steps for contaminating viruses (see ICH Q5A).

For a biotechnological IMP, due to the developmental nature of the manufacturing process and of the product, a reduced programme of validation studies on virus inactivation/removal may be appropriate compared with the data requirements for marketing authorisation. A reduced programme would only be applicable for cell lines classified in ICH Q5A as 'Case A' or 'Case B'. A reduction in the validation studies may also be relevant based on demonstrated in-house experience (see Section 4.4). Such in-house experience may also be applicable to the data requirements of an MAA; however, the guideline does not address this point. The following general factors should be considered in justifying the omission of any of the virus detection assays listed in Q5A and a reduction of product specific validation studies:

- the nature of the production cell line,
- the history of the cell line and its use,
- the extent of characterisation of the cell line,
- use or non-use of raw materials of human and/or animal origin during manufacture,
- potential exposure to adventitious contamination,
- the stage of development of the product,
- experience of the company with the cell line involved,
- experience of the company with specific inactivation/removal procedures to be used,
- published data.

In addition to the provision of data, a risk assessment should be made taking into consideration the above factors.

4.2 Assuring the viral safety of biotechnological IMPs

The principle of assuring the viral safety of a biotechnological IMP involves direct testing for viruses combined with validating the ability of the manufacturing process to inactivate/remove viruses as described in ICH Q5A. To date, transmission of a virus through the use of an approved biotechnological medicinal product has never been reported. In some cases, a viral contaminant has been detected during manufacture and these have generally arisen as an adventitious contaminant, deriving from biological material, e.g. serum, being used during fermentation.

4.2.1 Cell line qualification: testing for viruses

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.

A working cell bank (WCB) might only be set up during clinical development and thus, for some biotechnological IMPs to be used in Phase I/II trials, it may not yet have been established. When established, a WCB should be tested as outlined in Q5A.

Cells at their limit of *in vitro* cell age (end of production (EOP) cells) should be derived from the scale used for the intended clinical batch and similarly should be tested as per Q5A, unless otherwise

justified. Any change in the production process that results in an extension of the *in vitro* cell age, such as by the introduction of a WCB or by a change in scale, will require reassessment of EOP cells. Consequently, it may be useful for manufacturers, at their first assessment, to examine cells taken beyond their *in vitro* cell age in order to allow expansion of the cells during development.

Since endogenous retroviral viruses or particles are present in most cell lines currently in use and there is a probability that they will be present in a novel cell line, particular attention should be paid to investigating the cell line for their presence.

Where a validated in-house cell bank is used by a manufacturer to derive individual cell lines expressing different biopharmaceuticals, viral safety information for that cell bank (e.g. data on susceptibility to a wide range of viruses) can contribute to the overall virus safety evaluation.

The replacement of *in vivo* tests such as MAP/HAP/RAP tests by *in vitro* testing for the exclusion of specific adventitious agents, e.g. by validated PCR or cell-based assays, is being investigated by several manufacturers. Such an approach is not peculiar to assuring the viral safety of IMPs but would be applicable also to an approved product and ultimately will require full validation of these alternative tests and a general acceptance of them by regulatory agencies.

4.2.2 Testing for viruses in unprocessed bulk

Independent of the stage of development, the unprocessed bulk should be tested as defined in ICH Q5A including quantification of retroviral particles, where applicable. It is recognised that, early in clinical development, the number of batches that have been manufactured may be less than the minimum number stated in Q5A that should be tested, i.e. at least three batches. The source and viral safety of the raw materials used during fermentation should be taken into account when devising the unprocessed bulk testing.

4.2.3 Validation of virus inactivation/removal

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, that are known to be present. For IMPs, a case-by-case approach will be required taking into account the characterisation of the cell line, the viral safety of raw materials as well as the nature of the process steps that may be effective in inactivating/removing viruses. Even when no raw materials of biological origin have been used and the cell line is fully tested, viral validation studies will be required as extensive testing cannot guarantee the viral safety due to limitations in viral detection assays. Full viral validation according to Q5A should be initiated as soon as the final production and purification process has been established and should be completed prior to use of the investigational medicinal product in Phase III studies, unless otherwise justified.

Validation should be performed according to the principles of Q5A although a demonstration of robustness may not be warranted at early stages of clinical development. The relevant steps in product purification that contribute to virus clearance should be described and their capacity 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. The CHMP Note for guidance on virus validation studies (see references) also provides useful detailed information on such studies.

4.2.4 Validation of materials for Phase I and II studies

Prior to Phase I studies, 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. Case B cells (as defined in Q5A) contain endogenous retroviral viruses or 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.

Regardless of the extent of direct virus testing of the production cell line, 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 have been or are being used during cultivation of the production cells. Potential contaminants may be enveloped and non-enveloped viruses. Consequently, prior to Phase I studies, for both Case A (no viral contaminant has been identified) and Case B cells, the process should be evaluated for the inactivation/removal of an enveloped virus (a retrovirus for Case B) and a small non-enveloped virus, unless otherwise justified. Two orthogonal steps should be assessed, if possible.

In performing the validation study, the limits of (i.e. worst-case) process parameters should be used.

The following circumstances might be used to support a reduced programme of validation studies:

- The extent of use/non-use of materials of biological origin during the development of the production cell line and during production itself.

- 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. 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. However, 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 factors do not affect virus reduction. Published data are especially unreliable where the removal of viruses is virus specific or not predictive in general, e.g. chromatography.

- Prior experience of the manufacturer with a specific downstream processing step. In the event that a manufacturer is developing similar type of products by established and well-characterised procedures, validation data derived for these other products might be applicable to the new product for an equivalent processing step.

  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, virus reduction should be equally effective 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 clearance data of a particular purification step would be possible when the product has similar biochemical properties and is purified by identical methods. The manufacturer should provide a critical analysis of the manufacturing step, such as, for nanofilters – type of filter, load per filter area, flow rates, pressure, composition of product intermediates, etc., or for chromatographic methods – column dimension including bed height, load, composition of buffer and product intermediates, linear flow rates, etc. 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 minimum, 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.

Due to the use of dedicated columns and the comparably small number of batches manufactured during early stage development, column re-use and sanitisation studies are generally not required for Phase I and II material. However, they will be expected in the MAA.

4.2.5 Validation of materials for Phase III studies

Full viral validation according to Q5A should be initiated as soon as the final production and purification process has been established and should be completed prior to use of the product in Phase III studies, unless otherwise justified.

4.2.6 Validation of Analytical Procedures

For Phase I/II clinical trials, the suitability of the analytical methods applied for viral testing should be demonstrated. A tabulated summary of the results of the validation, carried out according to ICH-methodology, should be provided (e.g. results of values found for specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate). It is not necessary to provide a full validation report.

Viral tests performed in accordance with the European Pharmacopoeia are normally not (re-) validated by the company.

In addition to the information to be provided for Phase I/II trials, for Phase III studies a full validation report should be held available and should be submitted upon request.

4.3 Virus safety risk assessment

The decision to authorise a clinical trial from the viral safety point of view should be based on the risk/benefit situation. Thus, in addition to the derivation and provision of raw data on the viral safety of the manufacturing process, a risk assessment should be provided with an application for clinical trial authorisation, taking into consideration the factors noted above in Section 4 and the points outlined in Section 4 regarding characterisation of the cell line and validation of inactivation/removal. The indication, the dose, the frequency of administration, the number of people exposed and the study duration will also impact on the risk assessment. It should be noted that the immunological status of the Phase II and Phase III trial group may differ from those in the Phase I group.

The risk assessment should be based on the calculation of estimated particles per dose (see ICH Q5A, appendix 5) and encompass all steps of the production process. In early development, the assessment of virus reduction may also be based on in-house experience. In late stage development, the calculation should put emphasis on product-specific study data; however, support from in-house experience may be added.

As outlined in ICH Q5A, the limitations of viral clearance studies and the underlying statistics should be considered and put into relation with other parameters such as indication, (e.g., immune response status of the patient, oncological indication), route and frequency of administration, and duration of treatment.

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

4.4 Re-evaluation of viral safety during development

Process changes are often introduced during development. Whenever significant changes in the cell culture system, cell generation level or in the manufacturing process are made, the effect of that change, both direct and indirect, needs to be considered in a virus safety risk assessment. According to the risk assessment, additional virus studies may be needed.

The manufacturer should document the changes made to the production process and perform a virus safety risk assessment as described above and provide the updated information for significant changes to the relevant authorities. New validation studies may be required.

Care should be taken in the introduction of any specific viral inactivation/removal steps during development to avoid any detrimental effect on the quality of the product.

4.5 Format of clinical trial authorisation documentation

The overall programme of assuring viral safety should be carefully and clearly presented with explicit justification for any reduction in testing.

The format, as required by the "Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial" includes a specific attachment, i.e., Attachment 2: 3.2.A Appendices, 3.2.A.2, Adventitious Agents Safety Evaluation, dedicated to the data on virus safety of biotechnological IMPs. All the data should be brought together in this Attachment in order to be self-standing and understood in its entirety without other sections of the main dossier having to be consulted. The level of detail should be adapted to the stage of development. It should be noted that raw data or full reports might be required. When the applicant makes use of generic data (i.e. data from other products), an adequate package of data should be provided to allow an assessment of the generic data and to provide confidence that these data are valid or supportive for the specific product under development.

For general consideration on virus safety documentation, information to be submitted should (or can) take into consideration the items stated in volume 2B of the Notice to Applicants, Part II V: v*irological documentation*[1].

Particular attention should be paid to raw material of biological origin for which a complete and detailed documentation should be provided.

REFERENCES (scientific and / or legal)

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

ICH Q5A: ICH harmonised tripartite guideline on Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin

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)

Volume 2B of the Notice to Applicants, Part II – IX. concerning chemical, pharmaceutical and biological documentation for biological medicinal products, Part II V: virological documentation (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/b/pdfs-en/part2_3en.pdf)[1]

[1] Corrigendum: mistake in reference to Notice to Applicant was corrected