20 December 2006

European Medicines Agency (EMEA)
7 Westferry Circus
Canary Wharf
London E14 4HB
United Kingdom

SUBMISSION OF COMMENTS ON GUIDELINE ON VIRUS SAFETY EVALUATION OF BIOTECHNOLOGICAL INVESTIGATIONAL MEDICINAL PRODUCTS - EMEA/CHMP/BWP/398498/2005

ISPE is pleased to provide comments on the above Guideline which have been compiled by the Regulatory Sub-Committee of the EU Investigational Products Group.

We would much appreciate that the comments and issues detailed in the document are addressed.

Yours sincerely,

Robert P. Best
President/CEO, ISPE

ISPE Headquarters
3109 W. Dr. Martin Luther King Jr. Blvd. | Suite 250 | Tampa, FL 33607 | USA | TEL +1-813-960-2105 | FAX +1-813-264-2816
www.ispe.org

European Medicines Agency

SUBMISSION OF COMMENTS ON GUIDELINE ON VIRUS SAFETY EVALUATION OF BIOTECHNOLOGICAL INVESTIGATIONAL MEDICINAL PRODUCTS - EMEA/CHMP/BWP/398498/2005

COMMENTS FROM Investigational Medicinal Product Group (IMPG) Regulatory Sub Committee of ISPE

GENERAL COMMENTS

The IMPG Regulatory Sub Committee welcomes the opportunity to comment on this proposed guideline. It supports the requirement to assess the need and extent of viral safety studies through the different stages of development. The focus of the guidance should be on ensuring the safety of investigational medicinal products. Although this guideline is primarily directed at phase I and phase II product, there needs to be more guidance on the studies required for phase III products. Statements that studies are "essentially as described in ICH Q5A" are not helpful and further clarification is required. Recognition should also be given that the strategy taken for phase I and phase II products may be very different for phase III products.

In places, the guideline does not provide specific enough guidance to some issues and therefore leaves room for interpretation. The BWP expert working group may consider an approach similar to ICH Q5A, where the body of document provides general guidance and specific examples are provided in an appendix/addendum to the main guidance

Additional clarity needs to be given on which studies need to be completed before the start of the phase III program and those studies that can be completed during the development program, so that they are complete prior to the submission of the Marketing Authorisation Application.

Where products are excluded from the guidance (e.g. product containing recombinant viruses) there should be a statement as to where appropriate guidance can be found or if guidance is going to be prepared.

The term Investigational Medicinal Product (IMP) should be used throughout where referencing the Clinical Trial Directive in context of clinical studies, terms such as "materials used" in trial requiring manufacture to GMP is misleading- only IMPs as defined in CTD are mandated to be made to GMP.

Section 4.2.1 The use of the ICH Q5A that was developed for commercial biopharmaceutical products approximately 10 years ago as a guideline for safety testing for clinical products does not take into account the more current ICH Guideline Q9 that approaches safety evaluation from a risk assessment approach. Given that there has never been a virus contamination of a biopharmaceutical product and that the standard cell lines used (e.g., CHO) in this industry have approximately 20 years of virus testing experience the conservative approach developed in Q5A may now not be appropriate. This is especially applicable for the limit of in vitro cell age testing where there is no data that demonstrates that as production cells age they become more susceptible to virus contamination. A risk based approach to cell bank testing should be employed in this guideline where the cell bank type and industry experience be used to determine the extent of testing required for clinical trials.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 95
E-mail: mail@emea.eu.int http://www.emea.eu.int

Section 4.2.4: We agree with the paragraph beginning with: "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". This is consistent with our definition of a "robust" viral clearance step, which is a requirement for modular approach.
As indicated in different chapters of this draft guideline (Section 4.1, 4.2.2, 4.2.3 and 4.3) the viral safety evaluation for biotechnological medicinal products should take into account assessment of the biological raw materials (especially animal or human derived) used in production. To date, within EU Health Authorities, there exists a wide interpretation of requirements associated with raw materials of biological origin. The current guideline should also address this topic considering risk-based approaches for early development regarding type and origin of raw material, its process conditions and testing, as well as its use in the manufacture of the medicinal product.

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no[1]. + paragraph no.	**Comment and Rationale**	**Proposed Change (if applicable)**
Section 1 Introduction 2nd and 3rd paragraph	Replace "materials" used in trials with IMPS, as only IMPS, defined in Clinical Trial Directive, are required to be made to GMP. Similarly replace "products" with IMPs.	Ensure correct terminology throughout the document where using IMPs as defined in Directive 2001/20/EC.
Section 2, Scope 2nd paragraph	Provide clarification where guidance for products excluded from this guide and used in clinical trials, may be found, e.g. for products that contain recombinant viruses.	If it is intended to issue such guidance at a later date, then this should be stated..
2. Scope, 3rd paragraph, 2nd sentence	Validation is typically done when the final manufacturing process is developed, which may occur prior to during Phase 3.	Suggest replacing …"for Phase III materials" with …"during Phase III," validation studies should be performed as described by ICH Q5A (see section 4).

[1] Where available

Section 2 Scope 3rd paragraph	Clarify what validation studies “essentially the same“ as described in ICH Q5A means. It is unlikely that all studies will be completed at the time of commencing Phase III clinical studies.	
Section 4.1 2nd paragraph (i)	Delete “all” raw materials and replace with “animal derived “ raw materials or use the words “as appropriate. Such testing for all raw materials is not relevant e.g. inorganic salts. ICH Q5A allows for appropriate treatment (e.g. heat) of raw materials in lieu of testing.	Use the phrase “animal derived raw materials” rather than “all raw materials”
Section 4.2, last phrase	Clarification as suggested. Add reference to relevant guidance regarding serum and viral testing.	Change “e.g. serum, being used during fermentation” to “e.g., “if serum is used during fermentation” Add reference to guideline for serum: CPMP/BWP/1793/02.
	Also in this section, there is a huge jump from Phase I and Phase II materials to expectations in MAA. Further guidance for Phase III is recommended.	

Section 4.2.1 Paragraph 3 sentence 1	*"Cells at the 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".* The expectation of this draft for Phase I/II trials is to have full cell line testing done on cell banks, regardless of their stage of development. The Q5A bases the testing requirements on the stage of development of the product, whereas, this draft guideline does not. Our concerns with the draft guideline are two fold; 1) the expectation of a set cell culture manufacturing process early in development and 2) that there would be extensive testing required between each production run, if any changes are made during development. Neither one of these scenarios are in alignment with clinical product development. Clinical runs can have varying cell ages between production runs; and as the draft guideline states each time there is an extension of the cell age the limit of *in vitro* cell age studies must be repeated. These studies would require 4-6 months of testing because these assays include in vivo studies and co-cultivation studies for retroviruses. There can be many production runs during the clinical development process with possibly each one with of increasing cell age. Considering, that to date, transmission of a virus through the use of an approved biotechnology medicinal product has never been reported the requirement for full testing at the limit of in vitro cell age is disproportionate and unnecessary with regard to ensuring patient safety. On the other hand, it generates a high additional burden for industry developing products for early clinical trials. For EOP cells we suggest that a risk-based approach to viral safety testing is applied taking into account the nature of the cell line and its susceptibility to harbouring infectious retroviruses as well as the in house experience of the company with such cells. This should apply likewise for testing of EOP cells to qualify a WCB if this WCB is established during early clinical phases, i.e. prior to Phase III. In this context, we suggest that additional testing at the EOP cell level should be suspended for well-characterized cell lines especially CHO	Suggest to revise paragraph 3, sentence 1, as follows: "Viral safety testing at the end of production should follow a risk-based approach taking into account the nature of the cell line used, its susceptibility to harbouring infectious retroviruses as well as the in house experience of the company with this cell line. In general, ICH Q5A should be consulted in the setup of testing regimen, although full Q5A conformant testing may not always be warranted in early development stages (clinical phase I and II). The company should provide a rationale for its testing approach.

	cells that have for more than 20 years demonstrated to not harbour an infectious retrovirus. Adventitious viral safety testing is sufficiently covered by routine testing at the unprocessed bulk level. For other cell lines such as NS0 cell lines, we propose an appropriate testing regimen particularly focused at endogenous retroviruses. The requirement to using the "same scale" as used for the clinical batches goes contradicts with the requirements outlined in Q5A, where it is stated under 3.) that "The limit of in vitro cell age used for production should be based on data derived from production cells **expanded under pilot-plant scale or commercial scale conditions** to the proposed in vitro cell age or beyond." . Using production scale is not generally regarded necessary and should, therefore, be deleted from the guideline.	
Section 4.2.1 Paragraph 3 sentence 2	*"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 change in scale, will require re-assessment of EOP cells".* Although every change needs to be assessed for impact, not all changes will result in the need to reassess the EOP cells. Assessment of changes should be more general and not be restricted to extension of *in vitro* cell age alone.	Suggest to revise as follows: Any significant change in the cell bank system or the cultivation process may require a reassessment of the viral safety of the product and may entail partial or full retesting at the end-of-production level.
Section 4.2.1 Paragraph 6 sentence 2	*"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."*	Suggest to revise as follows: Such an approach is not peculiar to assuring the viral safety of IMPs but would be applicable also to an approved product and requires full validation of these alternative tests. Otherwise, please state what will define general acceptance of PCR or cell based replacements for MAP/HAP and RAP.
Section 4.2.1 last paragraph	Applicable to an approved should be deleted, as the scope of this document is not for approved products. More clarification and conclusion in this paragraph is needed.	Delete phrase "but would be applicable also to an approved product and"
4.2.2	i.e., at least three batches	Change to i.e., three batches

Section 4.2.3 1st paragraph	The guide states that full validation studies should be completed prior to use in Phase III studies. This is inconsistent with 4.1 3rd para, which states "a reduced programme may be appropriate ….compared with data requirements for marketing authorisation". Further guidance is required as "full" validation at the end of Phase II is not likely.	
Section 4.2.3, Paragraph 2, first sentence	*''Validation should be performed […] robustness may not be warranted at **early stages** of clinical development."* It is assumed that the term "early stage" refers to clinical phases I and II.	Please specify and/or add glossary
Section 4.2.4	Flexibility to re-use columns should be encouraged for Phase I and II. The statements "not generally required" should be deleted and reworded.	Should state, "During early stage of development columns may be re-used and appropriate studies, including sanitisation, should be undertaken and justified.
Section 4.2.4, 2nd paragraph	Enveloped virus is a vague term.	Add after enveloped virus "e.g., XMuLV" and include reference to Q5A Appendix 2, Table A.1"
Section 4.2.4, second bullet	Published data should be used when applicable.	Delete last sentence
Section 4.2.4 third bullet, second paragraph	Critical parameters are most important in the strategy referenced. A modular validation approach should be possible.	Suggest replacing "Processing prior to the specific step for the new and the established product(s) should follow a similar strategy" to "The critical process parameters to a specific step for the new and established product(s) should follow a similar strategy."

Section 4.2.4 Paragraph 2 sentence 4	*''Two orthogonal steps should be assessed, if possible''.* For small, non-enveloped virus inactivation/removal, one process step is sufficient if effective removal can be demonstrated. Otherwise, an additional step needs to be validated.	Replace "if possible" with "where a single step is shown to be ineffective."
Section 4.2.4 Paragraph 3	*''In performing the validation study, the limits of (i.e. worst-case) process parameters should be used''* There are few manufacturing runs at clinical stages, and those runs are performed at target conditions. The understanding of design space and the robustness of the separation is sufficient to establish "worst case" during early clinical manufacturing. Furthermore, in some cases it is difficult to establish the scientific basis for "worst case".	Replace "the limits (i.e. worst-case) process parameters should be used" with "target process parameters should be used. It may be advisable to use worst-case conditions where applicable (e.g., usage of the highest pH realised in the manufacturing process for virus inactivation).
Section 4.2.4 paragraph 4 bullet 2 sentence 4	*''Published data are especially unreliable where the removal of viruses is virus specific or not predictive in general, e.g. chromatography.''* We agree with the draft document on limited use of published data to support modular viral validation. Published data usually does not provide sufficient information on all of the process parameters for a unit operation. This data should not be used alone to support reduced validation program. In-house data, where all of the process attributes and parameters are thoroughly understood, can provide the complete confidence that the new product/process will clear virus to the same extent as the previous product. However, the last sentence stating that virus removal by chromatography is virus specific or not predictive in general is contradictory to Q5A. VI.C. Paragraph 4, which is a science and risk, based evaluation of virus removal by separation steps, such as chromatographic procedures.	Replace with "Published data alone are not sufficient to support modular validation."

Section 4.2.4 paragraph 4 bullet 3 sub paragraph 3 sentence 1	*''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''.* In order to use modular validation, a defined set of scientific criteria on each type of unit operation must be met, which then leverages in house validation data from previous similar processes. Previous validation studies or design space studies for certain unit operation can provide data to define a design space.	Replace "purified by identical methods" with "purified by identical methods and/or similar process performance parameters i.e., within an established design space.
Section 4.2.4 last paragraph on page 6	The column re-use data is continually gathered post-approval, with extensions based on ongoing data.	Suggest changing the last sentence to "However, they will be expected in the MAA" to "a strategy for column re-use and sanitisation studies will be expected in the MAA with a commitment to collect data post-approval."
Section 4.2.5 "	Same rationale as for Section 4.2.3 above.	Delete "and should be completed prior to use of the product in Phase III studies, unless otherwise justified."
Section 4.2.5	*"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."* Reduced program of validation studies should be allowed for PIII, if supported by in-house data. Further column reuse and sanitization studies should not be required if limited product runs for PIII, or supported by in-house data. This is supported by draft guideline section 4.1, paragraph 3.	Replace "unless otherwise justified . . ." with "unless otherwise justified, based on relevant in-house experiences (see section 4.4)." Suggest adding clarification that column reuse and sanitization studies are not required for phase III, and should be provided in the MAA."
Section 4.2.6.	Validation of Analytical procedures of the viral testing is typically not included in a submission. ICH Q5A does not request validation of viral test methods.	Change Section name to 4.2.6 Qualification of Analytical Procedures. Delete entire section except second paragraph.

Section 4.3, paragraph 1, sentence 3-5	*"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.* *Additional clinical parameters may be of value and will be included in the risk assessment if applicable"* In accordance with Q5A the viral safety assessment should be based on three complementary columns: a) selecting and testing cell lines and other raw materials, including media components, for the absence of undesirable viruses which may be infectious and/or pathogenic for humans; b) assessing the capacity of the production processes to clear infectious viruses; c) testing the product at appropriate steps of production for absence of contaminating infectious viruses. Accordingly, the viral safety assessment required in this draft guideline should focus at these "quality related" aspects. Clinical parameters, such as dosing, patient number, study duration, change during development. Therefore, clinical parameters will usually not be (and should not be) the primary decision basis for the safety testing/validation programme determined for the product, and should not be required in the viral safety risk assessment, unless optionally, if deemed necessary/helpful by the company. The guideline requires to give an assessment of the immune status of the patients to have a better idea if the exposed patients are able to respond adequately to a viral infection induced by potential viral contaminants present in the product The immunological status of the patient population may vary among different studies and not only between phase I and phases II or III. In case of patient with weaker immune status, the probability of contamination by a virus of the environment is bigger than by the potential presence of virus in the biotechnology products.	Suggest revision as follows: In accordance with Q5A the viral safety assessment should be based on three complementary columns: a) selecting and testing cell lines and other raw materials, including media components, for the absence of undesirable viruses which may be infectious and/or pathogenic for humans; b) assessing the capacity of the production processes to clear infectious viruses; c) testing the product at appropriate steps of production for absence of contaminating infectious viruses. The indication, the dose, the frequency of administration, the number of people exposed, the study duration and the immunological status of the patients may also impact on the risk assessment and may be included in the risk assessment if considered applicable by the manufacturer. In this context, it should be considered that several of these parameters would change between Phase I, II and III. Additional clinical parameters may be of value and may be included in the risk assessment if applicable.

Section 4.3, paragraph 2, sentence 2	*''[…] 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 cell lines and validation of inactivation/removal.''* It is unclear what exactly is here being referred to. (factors noted under section 4.1 and 4.2.4?)	Suggest to revise as follows: […] a risk assessment should be provided with an application for clinical trial authorisation taking into account the factors noted under 4.1 (bullet list). Otherwise, please specify.
4.4, 1st paragraph, last sentence	New validation studies are not required unless the small-scale model is no longer applicable.	Change "additional viruses studies may be needed" to "additional virus testing may be needed if the small scale model is no longer applicable."
Section 4.4, paragraph 2-3	*"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."*	Examples of changes that would require a company to undertake additional virus studies may be helpful, e.g. via an appendix as indicated under "General comments".
Section 4.4 last paragraph	Not applicable.	Delete last paragraph
Section 4.5.	References to commercial guidelines is concerning at Phase 1/2 and may encourage MAA-level expectations on early development.	Add reference to serum: CPMP/BWP/1793/02.

Section 4.5 paragraph 2 , sentence 1	The risk assessment is study specific and not product specific anymore. If this risk assessment has to be included in the section 3.2.A.2., the technical filing has to be systematically updated for each application. Cross reference to previous submission is no longer possible. The viral safety validation in early phase is done once at the time where the clinical development program for phase I and II is not fully fixed. Might be not applicable	In case of abbreviated IMPD section (previous submission done with the same compound), only the viral safety assessment with an updated risk assessment could be needed in some cases?
Section 4.5, paragraph 2, sentence 4	*"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."* The statement "It should be noted that raw data or full reports might be required." does not give guidance as to when that may be the case. Companies need to know the circumstances under which these data will be required and the expectations of all agencies should be the same.	Please give examples (e.g., in a part of an Appendix) which raw data or full reports may be required.

Please feel free to add more rows if needed.

These comments and the identity of the sender will be published on the EMEA website unless a specific justified objection was received by EMEA.