



European Medicines Agency

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

COMMENTS FROM Parenteral Drug Association (PDA)/Richard Levy, Senior Vice President, Scientific and Regulatory Affairs

GENERAL COMMENTS

The draft guidance is much welcomed. It is well-written with the main concepts being clearly outlined.

We are, however, concerned that the document has an implied expectation that (1) cell culture manufacturing process are set early in development and do not evolve as the products proceed in development or (2) that extensive testing should be required between each production run, if even minor changes are made. Neither of these two scenarios is in alignment with the current practice of clinical product development. In reality, clinical runs of the same product in development can have varying cell culture lengths and concomitant varying cell age (measured as cell doublings). Changes are common because of increasing demand as products traverse phase 1 through 3, because of improvements in the cell cultures strategy that increase productivity, product uniformity and other quality attributes, and because of scale changes. 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; in effect multiple studies would need to be performed for each new product. Successful products can have many production runs during clinical development in order to meet the demands of large clinical trials; each one may have an incrementally increased cell age. These studies can require 4-6 months of testing because the assay panel includes *in vivo* studies and co-cultivation studies for retroviruses. We feel that this requirement would have the impact of discouraging cell culture process optimization, possibly even negatively impacting product consistency optimized during this development process.

We are also concerned about the stated requirement in draft guideline that viral clearance validation studies conforming to ICH Q5A should be performed prior to the use of investigational products in Phase III clinical studies. In general, full conformance with ICH guidance documents is an expectation for marketed, not investigational, products. We fully agree that viral safety is a very serious concern; this principle should not be compromised. However, the current industry practice for phase III trials does not include full conformance with each aspect outlined in ICH Q5A for virus clearance studies. Instead, industry takes a holistic approach for each investigational product by evaluating all the components of the viral safety program in place (e.g. careful raw material selection and testing, well characterized and tested cell lines, demonstration of robust clearance by the process of enveloped and non-enveloped model viruses, etc). Given the excellent safety record of industry as a whole in assuring the viral safety of investigational biopharmaceutical products, we feel that it is warranted to allow flexibility to conduct the Q5A viral validation studies during phase III clinical development instead, with the requirement to submit full reports later in the marketing authorization application.

Public

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>

©EMA 2006 Reproduction and/or distribution of this document is authorised for non commercial purposes only provided the EMA is acknowledged

Please consider the following additional points:

- Regarding the testing and validation requirements for phase III products, different sections of the document word EMEA's expectations differently. We provide examples of the different wording in our detailed comments below. Please consider unifying the language describing testing and validation expectations in the different sections of the draft.
- PDA welcomes the concept of in-house experience in the draft document. We feel that acceptance of in-house virus validation experience will streamline product development and improve product safety. Our one concern is that we feel that in-house data for chromatography steps is probably more robust and reliable than the draft document allows. We feel that manufacturers with extensive experience with virus removal by chromatography can provide examples of this robustness and reliability; we would welcome a more extensive discussion of this issue.
- We would like clarification about when raw data for virus testing and virus validation will be requested for submission. In our opinion, provision of raw data should be limited to special situations only, e.g., when a novel technique is used.

Concerning individual points outlined above, we ask the BWP to consider meeting with the representatives from PDA who contributed to these comments.

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no¹. + paragraph no.	Comment and Rationale	Proposed change (if applicable)
Page 7, section 4.2.5	<p>Issue 1: The expectations of the draft document will unnecessarily increase product development timelines by postponing the start of Phase III.</p> <p>The full viral validation studies per Q5A typically takes 9-12 months to complete from the point of collecting the representative material for the study from the Phase III campaign to the completion of all reports. In addition, review time by the Clinical Trial Application by the regulatory authorities will also postpone phase III by variable lengths of time, depending on the complexity of the submission</p> <p>Thus, to complete the study prior to the use of Phase III clinical material, sponsors will need to delay the start of their Phase III clinical program for a significant period of time. This requirement will be a significant obstacle to biopharmaceutical companies to bring innovative medicine to patients in a manner that best balances development time and safety of products.</p>	
Page 7, section 4.2.5	<p>Issue 2: To fulfil the expectations of the draft document, process experience currently gained in Phase III will need to be obtained prior to Phase III. Example is provided:</p> <p>If full Q5A virus removal validation is started as soon as the final production process is established, then the process that is used for the viral validation needs to be set before Phase III production experience is gathered. As of today, a Phase III process undergoes some amount of optimization and scale up. This optimization is carefully implemented on the basis of process performance, and</p>	

¹ Where available

	<p>extensive development studies which can be on-going during Phase III. The process is very likely to be further optimized based on actual experience generated from the full scale Phase III production. All of this optimization contributes to product safety and consistency, but is jeopardized if the initial phase III process is cemented in place because of regulatory concerns.</p> <p>Examples:</p> <ul style="list-style-type: none"> • Ratios of pre-filter and filter areas for a given process load might need to be adjusted based on actual scale data, • the protein concentrations of given column chromatographic intermediates might change, thus the ranges of product concentrations might not be set representatively until sufficient data generated from actual Phase III scale production become available. • In both cases, if full viral clearance validation data is needed prior to having the pivotal scale production experience, the scale-down model used for the viral validation would be unrepresentative of the actual commercial production. 	
<p>Page 7, section 4.2.5</p>	<p>Issue 3 (related with Issue 2): To fulfil the expectations of the draft document, virus removal validation studies will be needed ahead of other process validation activities, which can subsequently impact viral clearance if the process requires subsequent optimization.</p> <p>Upon seeing positive results from proof of concept Phase II clinical studies, firms initiate process validation activity in parallel with the Phase III clinical development. Prior to the Phase III clinical studies, the production process is typically not set and thus not yet ready for formal process validation. The actual production experience and process characterization are critical to define the range of process parameters.</p> <p>To meet the requirement stated in the draft guideline, the full viral validation would need to be conducted significantly ahead of other components of process validation, which is contrary to current world wide regulatory expectations.</p>	
<p>Page 7, section 4.2.5</p>	<p>Issue 4: Economic considerations can impact whether a product proceeds in the development pipeline.</p>	

Parenteral Drug Association (PDA) Comments on EMEA/CHMP/BWP/398498/2005 (Continued)

	<p>In many cases, for example for the oncology products, the clear commercial feasibility of a product is not determined until the Phase III clinical studies are completed. In these cases the requirement to commit the resources for viral validation before Phase III can be prohibitive from the economical point of view. By allowing flexibility in this area, product development for economically marginal products is encouraged. This is particularly important for products designed for orphan indications or indications more common in developing countries than industrialized nations.</p>	
<p>Page 7, section 4.2.5</p>	<p>Issue 5: The current safety record of biopharmaceuticals are excellent.</p> <p>Biopharmaceutical products have demonstrated superior viral safety record. Due to the extreme diligence from sponsors in implementing good practice in cell line and raw material testing, and building in robust viral clearance capability in their downstream processes, no adverse safety event related to viral contamination has yet occurred. In this context, there is no clear reason to change current regulatory expectations by requiring full viral validation ahead of Phase III clinical studies. We believe that this represents an undue burden to the biopharmaceutical industry and is not necessary to demonstrate an acceptable level of safety for clinical trial subjects.</p>	
<p>Page 7, section 4.2.5</p>	<p>Issue 6: The safety approach for biopharmaceuticals is multi-faceted and robust.</p> <p>The ability of the downstream process to clear enveloped and non-enveloped viruses is currently evaluated during early stages of development. This consideration should greatly reduce any potential safety concerns associated with the inadequate removal of endogenous or adventitious viruses after minor process changes. In this context, we feel that gathering of additional, secondary information as per Q5A full virus removal validation (e.g. additional models, column cleaning, viral distribution, etc) can be postponed until the marketing application stage without sacrificing the safety of clinical trial subjects.</p>	

<p>91</p>	<p>The guidance draft requests testing of EOP cells “unless otherwise justified”. However, the next sentence, implies that both WCB <u>AND</u> EOP have to be tested in that it sets up requirements that appear to ask for mandatory testing in two cases: if a WCB is set up or the manufacturing scale is changed. This requirement goes beyond ICH Q5A in that each new WCB would necessitate testing EOP. The language should be clarified. For example, the meaning of “reassessment” in this context is not clear. Does it really mean testing is mandatory or is a risk assessment is possible instead? An alternative wording for the paragraph is proposed which is meant to better describe the intention of the current wording. Please consider this together with the comment on line 95, which deals with changes during development.</p> <p>We make this comment in the context that to date, transmission of a virus through the use of an approved biotechnology medicinal product has never been reported. We feel that 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 should be applied instead taking into account the nature of the cell line and its susceptibility to harbouring infectious retroviruses. The risk based approach should also include 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.</p> <p>In this context we suggest that additional testing at the EOP cell level should be suspended for well characterized cell lines, especially CHO cells. CHO cells have been used by industry for more than 20 years and have been demonstrated to not harbour 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.</p>	<p>“...When established, a WCB should be tested as outlined in Q5A, chapter III A 2.”</p> <p>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 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 testing may not always be warranted in early development stages (clinical phases I and II). The company should provide a rationale for its testing approach.</p>
<p>93</p>	<p>The requirement to test EOP cells grown at the “same scale” as used for the clinical batches contradicts with the requirements outlined in</p>	

Parenteral Drug Association (PDA) Comments on EMEA/CHMP/BWP/398498/2005 (Continued)

	<p>Q5A. For example Q5A states under (3) that “The limit of <i>in vitro</i> 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 <i>in vitro</i> cell age or beyond.” .Growing EOP cells at production scale, even when it is a smaller clinical production scale, is not generally regarded as necessary and should, therefore, be deleted from the guideline.</p>	
95	<p>Although it is common industry practice to assess each process change for potential product impact; many changes undertaken during development are minor and not expected to impact the growth of viruses or the susceptibility of cells to viral infection. Thus, we believe that many changes can be made without a reassessment of the EOP cells. A risk based approach to this issue is warranted and the assessment of changes should be left more flexible and not be focused on the extension of <i>in vitro</i> cell age alone.</p>	<p>Suggest to revise as follows: A 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.</p>

Parenteral Drug Association (PDA) Comments on EMEA/CHMP/BWP/398498/2005 (Continued)

95	We have suggested revisions for the following language: <i>“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.”</i>	Suggest to revise as follows: Based on the risk assessment, it may be useful for manufacturers to examine cells taken beyond their in vitro cell age in order to cover further expansion of the cells during development. The risk assessment should consider the type of cell substrate used to produce the investigational product and the in-house experience of the firm.
102	A more flexible and clear definition of the "difference" of biopharmaceuticals should be provided. For example, if the same type of product, for example monoclonal antibodies of the same subclass, is expressed in the same transfected parental cell line, it seems excessive to test each new cell bank with the whole battery of assays on a product-by-product basis?	"...can contribute to the overall virus safety evaluation. I.e., if a series of monoclonal antibodies of the same subclass is expressed in the same parental cell line using the same transfection protocol under controlled conditions, testing for relevant viruses such as endogenous retrovirus and adventitious agents by in vitro co-cultivation methods only might be acceptable."
118	In the current draft, little flexibility from the described procedures appear to be allowed. This is the case even for IMPs which may be developed for illnesses where no cure exists. Ideally, virus safety should be evaluated in the context of the overall safety of the planned clinical study. In the draft document, this context is missing, potentially resulting in two different safety assessments. This is a significant disadvantage as compared to the approach in other regions of the globe, for example the US. The US PTC on Monoclonals allows such flexibility and should be considered by the BWP. Also the draft document only allows not having a final process at the start of phase III for special cases. This is not to be in line with ICH Q5A and S6. It also is unrealistic and not in accord with current industry practice. Changes - may they even be minor changes - are still made to e.g. the production process during phase III.	"Full viral validation according to Q5A should be initiated as soon as the final production and purification process has been established. This activity can occur concomitantly with phase III trials, but needs to be completed prior to submission of a marketing authorization. Refer to chapter 4.4 of this guideline."
123	It is important to clarify that full validation according to Q5A would not include resin reuse studies. This is acknowledged in section 4.2.4 last paragraph as not needed for investigational material, but would be expected in any MAA filed. These studies are not needed before the MAA as the relatively limited investigational product demand limits the number of lots produced to meet this demand and the consequent number of chromatography cycles	For "unless otherwise justified." suggest adding clarification "unless otherwise justified (as in column reuse and sanitization studies which would be provided in the MAA)."Specify text in following section 4.2.5 "Validation for phase III" accordingly to state that "full validation according to ICH Q5A should be [...] completed prior to use of the product in Phase III studies [...]. Column reuse and sanitisation studies are not required at this point in time. However, they will be expected in the MAA
131	A more clear definition of "early stage" is needed. We assume that the term "early stage" refers to clinical phases I and II.	Please specify and/or add glossary
151	<i>"Two orthogonal steps should be assessed, if possible"</i> . For small, non-enveloped virus inactivation/removal, it is often feasible to demonstrate the robustness of only one effective process step early	Replace "if possible" with "where a single step is shown to be ineffective."

Parenteral Drug Association (PDA) Comments on EMEA/CHMP/BWP/398498/2005 (Continued)

	<p>in development. We feel that at this stage, this should be sufficient if effective removal can be demonstrated. Otherwise a additional steps needs to be validated and demonstrated for robustness. This can be impractical as there are only a few manufacturing runs at clinical stages, and those runs are performed at target conditions.</p> <p>The understanding of design space and the robustness of the separation is sufficient to establish "worst case" during early clinical manufacturing. This information can be applied cross-products as long as the unit operation is understood from a mechanistic standpoint. Furthermore, in some cases it is difficult to establish the scientific basis for "worst case"</p>	
152	<p>We have limited knowledge of the "worst case parameters" for viral removal . It is inappropriate to assume that the worst case parameters for viral clearance are the same as those for step yield, peak resolution, etc. Determining this will require an extensive experimental effort, which while interesting from a scientific standpoint, is not practical on a product-by-product basis.</p>	<p>Delete: In performing the validation study, the known limits of (i.e. worst case) process parameters should be used. 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 and known (e.g. usage of the highest pH realised in the manufacturing process for virus inactivation)</p>
158	<p>We agree with the draft document on the preference of in-house data over published data to support modular viral validation. Published data does not always provide sufficient information on all of the process parameters for a unit operation. In cases where there is limited information on applicable process parameters, published data should not be used alone to support a reduced validation program, except in unusual cases such as exploratory clinical trials for immediately life threatening indications.</p> <p>In-house data, where all of the process attributes and parameters are thoroughly understood, can provide greater confidence that the new product/process will clear virus to the same extent as the previous product.</p> <p>However, we disagree with the last sentence stating that virus removal by chromatography is virus specific or not predictable in general. This is contradictory to Q5A. VI.C. Paragraph 4 which advocates a science and risk based evaluation of virus removal by separation steps, such as chromatographic procedures.</p>	<p>Delete last sentence of this paragraph.</p>
178	<p>We believe that the in house validation data concept, relies on meeting defined sets of scientific criteria for each type of unit operation. This then leverages in house validation data from</p>	<p>Replace "purified by identical methods" with "purified by identical methods and/or methods with similar process performance parameters, as justified".</p>

Parenteral Drug Association (PDA) Comments on EMEA/CHMP/BWP/398498/2005 (Continued)

	previous similar processes. Previous validation studies or design space studies for certain unit operation can provide data to define a design space. This design space can be applied to subsequent products with similar, but not necessarily identical unit operations	
191	Column lifetime studies are not necessary at the investigational stage and should be performed at the conformance lot stage instead, and monitored thereafter.	Due to the use of dedicated columns and the comparably small number of batches manufactured during investigational development, column re-use and sanitisation studies are generally not required for Phase I, II and III material. However, they will be expected in the MAA.
195	We believe that a reduced program of validation studies should be allowed for phase III, if supported by in-house data. Further column reuse and sanitization studies should not be required if there are only a limited number of product runs for phase III. Reuse/sanitization can also be 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 if only limited number of batches is made for phase III or supported by in-house data."
206	Regarding the sentence: <i>"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."</i> . We believe that submitting a summary of the validation data is sufficient to establish product safety, as long as the full report is available for inspection.	Replace "a full validation report should be submitted upon request." with "a summary of validation data should . . ."
210	This line appears to include a request for raw data. The justification for the raw data request is unclear in this context. The need for raw data review in the context of clinical studies should be justified and clarified. In addition, such requests contradict the previous section which allows for tabulated summary data.	Delete "raw" in front of raw data.
211	Regarding the sentence: <i>"[...] 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."</i> Please clarify which points are being referred to. Are they the 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).
248	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 and when not. Companies need to know the circumstances under which these data will be required in order to submit adequate dossiers. We also believe that harmonization of the expectations of regulatory agencies in this matter is desirable.	Please give examples (e.g., in a part of an Appendix) which raw data or full reports may be required. In case of abbreviated IMPD section (previous submission done with the same compound), is it possible that only the viral safety assessment with an updated risk assessment would be needed?

Parenteral Drug Association (PDA) Comments on EMEA/CHMP/BWP/398498/2005 (Continued)

	<p>The increasing trend in industry for risk assessment is toward study specific assessments and away from product specific assessments. If this risk assessment is to be included in the section 3.2.A.2.of technical filings, subsequent technical filings will need to be systematically updated for each new application. If this is the case, future cross references to previous submissions will no longer be possible. The current industry practice is to assess viral safety in early phase; this is done once and at the time where the clinical development program for phase I and II is not fully fixed. This complicates the continuity of risk assessments.</p>	
--	---	--

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