European Medicines Agency

London, 17 September 2008
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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON VIRUS SAFETY EVALUATION OF BIOTECHNOLOGICAL INVESTIGATIONAL MEDICINAL PRODUCTS

Table 1: Organisations that commented on the draft Guideline as released for consultation

Add name followed by link to individual received comment (upon publication by Web Services)

	Name of Organisation or individual	Country
1	Merck Sharp & Dohme (Europe) Inc.	Belgium
2	Biogen Idec	USA
3	European Generic Medicines Association (EGA)	Belgium
4	Lonza Biologics	United Kingdom
5	Investigational Medicinal Product Group (IMPG), subcommittee of the International Society for Pharmaceutical Engineering	USA
6	Cambridge Antibody Technology (CAT)	United Kingdom
7	Parenteral Drug Association (PDA) Europe	Germany
8	Regulatory Affairs & Biological Safety Consulting (RBS)	Germany
9	European Federation of Pharmaceutical Industries and Association (EFPIA) - European Biopharmaceutical Enterprises (EBE)	Belgium
10	Rentschler Biotchnologie	Germany

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Table 2: Discussion of comment

GENERAL COMMENTS – OVERVIEW	
Comment and Rationale	**Outcome**
Question to trade associations[1] **Under what circumstances, and why, it might be appropriate not to test EOP cells as recommended in the guideline.** Summary of position of trade associations: (PDA provided also comments in writing: see PDA comments for details).	**The industry felt that testing EOP cells as provided for in the draft guideline was overly burdensome for the information that it provide. The BWP agreed with this and has totally re-drafted the guidance provided for this issue.**
Question to trade associations **Under what circumstances, and why, it might be appropriate not to complete virus clearance studies prior to initiation of phase III studies; what particular aspects of Q5A need not be addressed at this point in time, and in the opinion of industry what minimum data would assure the viral safety of phase III material.** Summary of position of trade associations: (PDA provided also comments in writing: see PDA comments for details).	**Again, the industry felt it overly burdensome to provide virus clearance data at this stage of development especially as the final production may well not be in place prior to the start of phase III trials. Industry also provided their own views regarding the data that should be provided to assure viral safety. The BWP agreed with and adopted their views and revised the guidance accordingly.**

[1] On the basis of written comments received, further consultation of Industry via trade associations was undertaken through organisation of a scientific expert meeting on 12 September 2007 on the following topics:
- Under what circumstances, and why, it might be appropriate not to test EOP cells as recommended in the guideline.
- Under what circumstances, and why, it might be appropriate not to complete virus clearance studies prior to initiation of phase III studies; what particular aspects of Q5A need not be addressed at this point in time, and in the opinion of industry what minimum data would assure the viral safety of phase III material.
- The factors that should be taken into consideration in a risk based approach to assuring viral safety and the factors that are not pertinent.
- The application of a risk based approach for the viral safety of a novel cell line.
The following trade associations were invited: EFPIA/EBE, EuropaBio, PDA and EGA (EGA did not wish to participate).

Question to trade associations **The factors that should be taken into consideration in a risk based approach to assuring viral safety and the factors that are not pertinent.** Summary of position of trade associations: (PDA provided also comments in writing: see PDA comments for details).	**Industry provided their views on what risk factors should be taken onboard. They coincide closely with the views of the BWP.**
Question to trade associations **The application of a risk based approach for the viral safety of a novel cell line.** Summary of position of trade associations: (PDA provided also comments in writing: see PDA comments for details).	**Industry provided their views on what risk factors should be taken onboard for a novel cell line. They coincide closely with the views of the BWP and the guidance has been revised accordingly.**
Merck. The word "validation" is used in several contexts: (1) validation of viral clearance/inactivation; (2) validation of materials; (3) demonstration of the "suitability" of analytical methods for early phase materials for which a tabulated summary of the validation is to be provided; (4) full validation of viral detection analytical methods for Phase III. Perhaps the word "validation" should be restricted to very specific and generally recognized uses. Alternatively, it may help to define the word "validation" for the various contexts in which it is used (i.e. Validation of materials means…").	**Accepted and clarified in the revision.**
Merck. Titles to section 4.2.4 and 4.2.5 are unclear ("Validation of materials"?), and section contents appear to be special cases of the more general section on virus inactivation/removal 4.2.3. May we suggest sections 4.2.4 and 4.2.5 simply be renumbered as subsections of 4.2.3, so that it is clear that you are still referring to virus inactivation/removal studies as appropriate for either Phase I/II studies or Phase III studies. Alternatively, rephrase the titles of 4.2.4 and 4.2.5 using the same introductory title as 4.2.3, plus the Phase-specific modifiers.	**Accepted and clarified in the revision.**
EGA welcomes the initiative of the CHMP/BWP to develop a new guideline on virus safety evaluation of biotechnological investigational medicinal products. The draft guideline was read also in conjunction with guideline ICH Q5A (CPMP/ICH/295/95). ICH Q5A requires that the demonstration of reproducible clearance involving non-specific and specific models should include "at least two independent studies". We recommend including a similar recommendation to the draft guideline under consideration or clarifying potential discrepancies between the two guidelines.	**A similar recommendation has been included in the revision.**

IMPG: 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	**Comments have been taken into consideration in the revision. It was not felt that specific examples were useful.**
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.	**The approach to phase I, II and III has changed radically.**
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.	**Generally for products outside of the Scope, there is no guidance and the development of future guidance is unclear and so this has not been included in the revision.**
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.	**Note has been taken of the need to adhere to the use of the term IMP.**
IMPG: 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.	**A risk based approach is part of the guideline and the experience of industry with certain cell lines has been taken into account in the revision.**

IMPG: 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.	**No response required.**
IMPG: 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.	**This has been taken onboard and a risk-based approach is included in the revision.**
RBS 1. Principle considerations: • The guideline is highly welcomed. The virus safety assessment of IMPD's is differently handled in the individual Member States at present. It is therefore a great step forward if principles are defined that assure a harmonized methodology in the entire EU. The current draft of the guideline provides an approach to manufacturer's to use in-house data for demonstrating the virus safety of an IMP and defines criteria that can be applied to decide which data are relevant and applicable. This considers the current situation where virus safety data were generated in the last decade that might be applicable to new products if they are similar to previous products and if they are produced under similar conditions. This is a great step forward as well.	**No response required.**

RBS • The current draft of the guideline differentiates the requirements for virus validation studies for products in early and late phase of development. In referring to the requirements of the CPMP/ICH/295/95 (ICH Q5A) guideline when IMP's in late development are considered ('validation studies should be performed **essentially** as described by ICH Q5A') it remains unclear which data are required in the IMPD for phase III clinical trials and what is additionally be required for the MAA dossier. The request to provide a complete data package to demonstrate the capacity of the manufacturing process to remove/inactivate viruses according to ICH Q5A is not realised at present before phase III clinical trials are completed. It would be beneficial to extent the guideline in this point and provide clear guidance in differentiating between the requirements laid down in ICH Q5A for marketing authorization and the requirements that should be applied to materials in later stage of development (phase III). • It is mentioned that in-house virus validation data might be used for an MAA; it should be considered to allow the use of such data for clinical material in late development as well.	**Accepted. The revision has altered the recommendations considerably on this point.** **In-house data for clinical material is included in the guidance.**
RBS • Another concern is the qualification of the cell line for production of the IMP. Complete testing of EOP cells according to ICH Q5A is required in the draft guideline. This does not correspond to the test regime applied at present. As for virus validation studies, a stepwise approach for testing 'end of production cells'/'cells at the end of the in-vitro cell age' should be considered. In an early phase of product development MCB cells are cultivated for a relative short period of time; 'cells at the end of the in-vitro cell age' might be far away from 'end of production cells' (EOP) in an early stage of development. This is considered in the current draft where it is clarified that 'EOP cells should be derived from the scale used for the intended clinical batch'. The request to apply the requirements of ICH Q5A to these cells would require that the complete battery of tests is performed (infectivity assays for retrovirus and/or RT assay; TEM; in-vitro and in-vivo testing for adventitious viruses etc.). It would be helpful to provide clear guidance when the results of MCB testing are seen as appropriate in the early stage of development or when a complete or partial testing of EOP cells/cells at the limit of the in-vitro cell age according to ICH Q5A is required for phase I/II and/or phase III materials.	**Accepted. Guidance has been altered and clarified on this point.**

RBS 2. Some formal comments: • The abbreviation should be used consistently, i.e. 'ICH Q5A' or 'Q5A'. • The ICH Q5A guideline does not use the term 'validation' but uses the term 'evaluation'. This should be considered also in this guideline. • 'Robustness' in ICH Q5A considers the effectiveness of virus removal/inactivation stages for a broad range of viruses. If the term robustness is used in this draft guideline according to the definition of the CPMP/BWP/268/95 guideline, this should be clarified.	**Abbreviation use noted but not felt to be a problem.** **The term 'validation' (for viral clearance studies) has been avoided and clarified where used.** **'Robustness' term is used but not related to ICGH Q5A, and a brief explanation in the revision is provided.**
PDA: The draft guidance is much welcomed. It is well-written with the main concepts being clearly outlined.	**No response required.**
PDA: 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 though 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.	**Accepted and taken onboard in the revision.**

PDA: 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.	**Accepted and taken onboard in the revision.**
PDA: 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.	**Accepted and language issues addressed in the revision.** **It is felt that the revision adequately addresses the use of chromatography.** **The provision of raw data has been clarified in the revision (section 4.5).**
PDA: Concerning individual points outlined above, we ask the BWP to consider meeting with the representatives from PDA who contributed to these comments.	**This was undertaken.**

EFPIA & EBE support the development of guidance to facilitate the harmonisation of technical requirements required for studies to assess the viral safety of investigational medicinal products (IMPs). In particular the recognition in the draft guideline that a risk-based approach, where the potential safety risk of viral infection is balanced against the potential benefit of the therapy, the stage of development, the patient population, and other key factors, is very welcome. EFPIA & EBE also welcome the acceptability of a standardised "platform" approach to virus evaluation studies for investigational studies, where similar processes are used for similar types of products.	**No response required.**
It is recognised that some of the harmonised guidance provided in ICH Q5A *Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin* is relevant and applicable in part to IMPs, to differing extents depending on the stage of development. However the completion of viral safety evaluation studies conducted in accordance with the full scope of ICH Q5A is applicable to products only at the time of the Marketing Authorisation Application. Therefore the application of the requirements of ICH Q5A to IMPs in general is of significant concern to EFPIA & EBE members, particularly the expectation that its scope should be applied in full prior to initiation of Phase 3 studies, unless otherwise justified. This recommendation is of concern for two reasons: 1) It does not take into account the application of a risk-based approach based on the potential viral safety risk of the IMP which is advocated in other parts of the guideline and; 2) It limits the scope of the guidance on IMPs to Phase 1 & 2 clinical studies. The arbitrary differentiation between IMPs used in Phase 1 & 2 studies and IMPs used in Phase 3 studies is not considered appropriate, nor is it scientifically justified, as it takes no account of the potential risk of viral contamination of an IMP. More discriminatory guidance is necessary based upon the application of an appropriately qualified risk-based approach.	**Accepted. These criticisms have been taken fully into account in the revision.**
On a practical level, given completion of studies in accordance with ICH Q5A can normally only be conducted once the manufacturing process has been fully developed, and the fact that the Phase 3 manufacturing process is rarely identical to the final manufacturing process for commercial product supply, such a requirement would result in delays to initiation of Phase 3 clinical studies, and the duplication of many studies, with no demonstrable benefit to patient safety.	**Accepted/see above**
EFPIA & EBE members consider that the position outlined in the draft guidance with regard to expectations that Phase 3 studies be conducted in accordance with ICH Q5A is too restrictive. Further elaboration of the guidance is required to define the data expectations for inclusion in the IMPD for a Phase 3 clinical study for different scenarios based on the risk/potential benefit assessment.	**Accepted/see above.**
Detailed comments are provided below, and are ordered according to the priority: Critical, Major and Editorial. EFPIA & EBE members welcome the opportunity to further elaborate upon these comments.	

EFPIA/EBE (Ed) Throughout document **:** The term “fermentation” is typically associated with manufacture using microbial cell lines and should be replaced with “cell culture” to avoid confusion and to align with the scope of the guideline. Replace “fermentation” with “cell culture”.	**Done.**
EFPIA/EBE (Ed) Throughout document **:** The term “Validation” is present throughout the document, however is not used in Q5A. Replace the term “validation” with “evaluation” to be consistent with ICH Q5A. Replace “validation” with “evaluation”.	**Comment accepted. Usage of the term ‘validation’ has been addressed.**
MHRA: The document initially appears to be very prescriptive, particularly with regards the requirement for viral validation of phase III products being equivalent to that expected for products at time of marketing authorisation approval. It should be noted that products in phase III stage of development will not necessarily make it through to MAA, and that the potential expectation of a completed report of the full viral validation for a phase III product before the trial commences is likely to delay clinical studies and the late stage development programme. However, on closer reading, the prescriptive nature of the document is apparently undermined by the repeated use of the phrase 'unless otherwise justified'. This phrase removes the necessity for a number of defined requirements, in any number of undefined circumstances, hence rendering the document less helpful as a guideline. Finally it is generally observed that the document is sufficiently loose to allow continuing differences in MS requirements for viral safety evaluation of biotech IMPs and hence will not necessarily lead to increased harmonisation.	**The comment is no longer valid and the guidance on this aspect has been revised considerably.** **The phrase 'unless otherwise justified' is no longer used.** **The revised guidance should be more focused.**

SPECIFIC COMMENTS ON TEXT		
1. INTRODUCTION		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
IMPG Section 1 Introduction 2nd and 3rd	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.	**Done.**

paragraph	Ensure correct terminology throughout the document where using IMPs as defined in Directive 2001/20/EC.	
2. **SCOPE**		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
IMPG 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.	**No guidance is available and it is inappropriate to state what might be available in the future.**
IMPG 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).	**The guidance regarding when to conduct viral reduction studies has been revised.**
IMPG 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.	**The revision no longer makes this comment.** **Agreed and guidance revised with this in mind.**
RBS 2. Scope of the guideline	Third paragraph, 2nd sentence: Provided that the MCB was fully characterized according to ICH Q5A it should be allowed to apply an stepwise approach to cell line testing. It might be useful do cover the principle in this sentence keeping the more detailed information in chapter 4. **Current Text:** *However, it will be clear that the bulk of the guidance provided 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 text should be revised to the following**:	**Comment accepted. The revision no longer makes any such statement.**

	However, it will be clear that the bulk of the guidance provided is directed towards materials for phase I and II studies since for phase III materials the ICH Q5A guideline recommendations related to testing cells at the end of in vitro cell age and performing virus validation studies should be taken into account (see section 4). The guideline does not apply…	
EFPIA/EBE (Cr) Section 2 Paragraph 3 Line 35	"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)." This sentence should be deleted and Section 4 amended accordingly. ICH Q5A is intended to apply to commercial products, not to IMPs. Viral validation studies for the commercial manufacturing process are typically performed in parallel with Phase 3 studies, not prior to Phase 3. Delete sentence and amend Section 4 accordingly.	**Comment accepted. Sentence deleted and section 4 amended.**
EFPIA/EBE (Ed) Section 2 Paragraph 2 Line 30	"Thus, the guideline covers monoclonal antibodies and recombinant DNA derived products " Monoclonal antibodies are recombinant DNA derived products. Also, the scope should be clarified as to only cover vaccines obtained through recombinant DNA technology (recombinant proteins) and should clearly exclude inactivated vaccines and live attenuated vaccines. Replace with: "Thus, the guideline covers recombinant DNA derived products including recombinant protein subunit vaccines. ~~but does not apply to products that contain recombinant viruses such as vaccines or gene therapy products using viral vectors.~~ This does not include other types of vaccines such as inactivated and live attenuated vaccines and products that contain recombinant viruses such as gene therapy products using viral vectors. Products derived from hybridoma cells grown *in vivo* are also excluded from the scope of the guideline."	**This comment has been partially addressed in the revision. Monoclonal antibodies produced *in vitro* from hybridoma cells are not viewed by everyone as recombinant DNA products.**
EFPIA/EBE (Ed) Section 2	Reword statement "Viral safety requirements for all clinical development phases, from the first clinical studies in humans up to pivotal clinical trials, are addressed".	**Done.**

Paragraph 3 Line 34	Replace with: "This document outlines the viral safety requirements applicable to all stages of clinical development."	
4.1 GENERAL PRINCIPLES		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
Merck Page 4 Sec 4.1 line 4	Perhaps not all raw materials need be tested for viral contaminants. Consider rephrasing for clarity of expectations. Add "as appropriate" after "raw materials": … "thorough testing of the cell line and of all raw materials as appropriate"…	**Agreed and re-phrased as appropriate.**
EGA 4.1 para 1	The guideline states "the aim of virus safety studies for biotechnological IMPs is to demonstrate an acceptable level of safety for clinical trial subjects" We would welcome the elaboration of the term "acceptable level".	**Not addressed as too subjective/impossible to define, but should be clearly understood by all.**
IMPG 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"	**Comment accepted. This has been re-phrased as appropriate.** **Comment accepted. A risk-based assessment of raw materials of biological origin has been introduced (4.2.2).** **Comment accepted. This issue has been addressed.**
RBS 4.1.General principles	As a general principle, a stepwise characterisation of the cell line used for production should be accepted. If so, the proposed paragraph should be inserted after the second paragraph **It is proposed to insert this text as an additional paragraph after the second paragraph:** Cell line qualification is needed. It requires testing of the MCB according to ICH Q5A as well as testing of cells at the end of the in-	**Comment accepted. These issues have been addressed in the revised guideline.**

	vitro cell age (end of production cells (EOP) see 4.2.1.). The testing program for EOP cells should be defined considering (a) the stage of development, (b) the use or non-use of animal derived raw materials during cell cultivation, (c) other risk factors for contamination if identified and (d) the in-house experience with the cell line. The defined program for cell line qualification must be justified as described in Section 4.2.1.	
RBS 4.1.General principles	The current third paragraph should end after the third sentence and a new paragraph should be started with the fourth sentence because it covers both, cell line testing and virus validation studies. However, the guidelines did not address this point. The following general factors should be considered in justifying the omission of any of the ….	**Comment accepted. These issues have been addressed in the revised guideline.**
EFPIA/EBE (Maj) Section 4.1 Paragraph 2 Line 49	*"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)."* ICH Q5A does not require "thorough testing of all raw materials" – only those of animal or human origin. Additionally, by appropriate selection of raw materials, where other techniques are used to assure suitability (e.g. heat treatment), additional testing of raw materials may be reduced or not be necessary. Align with Q5A and clarify: a) selecting and testing cell lines and other raw materials (of human or animal origin), 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.	**Comment accepted. This has been addressed in the revision and aligned with Q5A.**
EFPIA/EBE (Maj) Section 4.1,	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	**Comment accepted. This has been taken on board and addressed in the revised guideline.**

4.2.2, 4.2.3 and 4.3	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. Add statement to 4.2.4 "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. A risk-based assessment focusing on the type and origin of raw material, its process conditions and testing, as well as its use in the manufacture of the medicinal product, is an acceptable approach to the assessment of viral safety".	
EFPIA/EBE (Ed) Section 4.1 paragraph 3 Line 56	Further clarity is required outlining the cases where a reduced programme is appropriate. Remove cross-reference to Case A and B and replace with explicit text.	**Comment accepted. The appropriate text has been clarified although retaining reference to Case A and Case B; it was not felt necessary to provide explicit text.**
EFPIA/EBE (Ed) Section 4.1 paragraph 3 Line 57	Correct cross reference to Section 4.2.4 "A reduction in the validation studies may also be relevant based on demonstrated in-house experience (see Section 4.2.4)."	**Cross reference is not felt to be necessary in the revised text.**
EFPIA/EBE (Ed) Section 4.1 paragraph 3 Line 57	"Such in-house experience may also be applicable to the data requirements of an MAA; however, the guideline does not address this point." This statement is outside of the scope of the proposed guideline and should be deleted.	**Comment accepted. Statement has been deleted.**
EFPIA/EBE (Ed) Section 4.1 paragraph 3	"potential exposure to adventitious contamination" It is unclear how assessment of potential exposure to adventitious contamination would be assessed. Clarity is required, or otherwise the bullet point should be removed.	**Potential exposure to the environment e.g. operators could occur when materials are not wholly contained in sealed units. It was not felt necessary to expand on this bullet point.**

Line 65	Further clarity is required, or otherwise the bullet point should be removed.	
4.2 VIRAL SAFETY		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
IMPG 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.	**Comment accepted. This text is removed in the revision and reference added.**
IMPG	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.	**Comment accepted. This precise text is removed and the point is addressed further in the revision.**
4.2.1 CELL LINES		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
BIOGEN 4.2.1	Section 4.2.1 states that end of production (EOP) cells should be "tested as per Q5A, unless otherwise justified". Please clarify what studies would be required in order to justify the absence of EOP cell testing. Specifically, if enhanced screening of each bioreactor harvest will be required, what would the testing be required to encompass. Definition of the studies required to justify the absence of EOP cell testing	**Comment accepted.**
LONZA Section 4.2.1/ paragraph 3/	Further clarification is sought regarding the terminology used in this section which makes reference to "**limit** of in vitro cell age/end of production (EOP) cells". According to our understanding these terms can mean different things.	**Comment accepted. This has been addressed and clarified in the revision.**

line1	The glossary in ICH Q5A defines in vitro cell age as *"A measure of the period between thawing of the MCB vial(s) and harvest of the production vessel measured by elapsed chronological time in culture, population doubling level of the cells or passage level of the cells when sub cultured by a defined procedure for dilution of the culture"*. Cells at the **limit** of in vitro cell age, are generally understood to be cells taken beyond their in vitro cell age (ie beyond the routine age of a typical culture) at a maximum generation number validated for the production purpose. Whilst no definition can be found for "end of production cells (EOP)" it is our understanding that EOP refer to those cells present in the culture at or just prior to harvest. Therefore EOP cells may or may not be cells at the limit of in vitro cell age. Further clarification regarding the terminology used would facilitate a better understanding of the guidance document, specifically with respect to the point at which virus testing of the cell line should be performed.	
LONZA Section 4.2.1/ paragraph 3/ line 5	Whilst a key driver of this guidance document is risk management, it is unclear whether the guidance is recommending that for all cell lines used in clinical studies, cells beyond their in vitro cell age/cells at the limit of in vitro cell age should be fully characterised as per ICH Q5A. Would partial or indeed no virus characterisation of cells beyond their in vitro cell age be permitted provided an appropriate risk assessment has been performed and the absence of such testing is justified based on previous experience and/or knowledge of the cell line?	**Comment accepted. This has been addressed and clarified in the revision.**
LONZA Section 4.2.1/ general	No distinction has been made in the guideline between the testing performed on a cell line used in a continuous process and that used in a batch process. Clarification on this point would additionally facilitate a better understanding of the appropriate point at which virus testing of the cell line should be performed. For example some virus tests may require viable cell cultures (eg TEM) therefore for a batch process, cells taken at or just prior to harvest when the viability is low are not suitable. Some flexibility regarding the point at which virus testing is performed is therefore requested	**Comment accepted. This has been addressed and clarified in the revision.**
IMPG 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	**Comment accepted. This has been addressed and clarified in the revision.**

	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 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. 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.	
IMPG 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.	**Comment accepted. This has been addressed and clarified in the revision.**
IMPG 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*	**The revised guideline avoids making reference to what might be required for approval of a product – where the draft version did so, there was criticism of this. Qualification of analytical procedures is addressed in 4.2.5.**

	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.	
IMPG 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"	**Comment accepted. The revised guideline now avoids making reference to what might be required for approval of a product.**
CAT Section 4.2.1/ paragraph 3/line 1	Clarification is sought of the intention of this section which refers to testing for viruses, as per ICH Q5A, of "Cells at the limit of *in vitro* cell age (end of production [EOP] cells)…". According to our understanding, these are different entities. Cells at the limit of *in vitro* cell age are those cells at the maximum permitted generation number for production supported by validation data. On the other hand EOP cells are those in the culture medium at the time of harvest. Such cells may, or may not, be at the limit of *in vitro* cell age. We believe the intention is to permit ICH Q5A testing of cells either at the end of production or at the limit of *in vitro* cell age. Cells at the end of production [EOP] or preferably cells at the limit of *in vitro* cell age should be derived from……	**Comment accepted. This has been addressed and clarified in the revision.**
CAT Section 4.2.1/ add new sentence to the end of paragraph 4	For the purposes of detecting endogenous virus or viral particles, there may be value in testing production cells during fermentation at the time of their peak viability. This is because certain viral tests such as reverse transcriptase detection are more sensitive at this stage of cell life. Furthermore, when cells are at low viability, such as at EOP or at the limit of *in vitro* cell age, there may be interference by e.g. DNA polymerase, which could lead to false positive results. For the purposes of optimising virus detection, consideration should be given to the testing of production cells during fermentation at the time	**Comment accepted. This has been addressed in the revision.**

	of their peak viability.	
RBS 4.2.1. Cell line Qualification third paragraph:	It should be considered to implement here requirements for the different level of testing in early/late clinical development. It seems possible to refer to the risk-based approach or to provide very detailed guidance in this section. This requires however a more detailed discussion. The proposed text provides only a wording for a more general approach in listing the aspects which should be considered. **Proposed Text:** *End of production (EOP) cell should be derived from the scale used for the intended clinical batch and similarly should be tested as per Q5A, unless otherwise justified.* A risk based approach should be applied in defining the test regime considering (1) the nature of the cell line and presence of infectious retroviruses, (2) the use or not-use of animal or human derived materials during cell cultivation, (3) the stage of product development as well as (4) the in-house experience with such cell lines.	**This has been addressed in the revision.**
RBS 4.2.1. Cell line Qualification fourth paragraph	The current fourth paragraph covers a general issue namely the importance of considering contamination with retrovirus. This paragraph should therefore be re-located. It should be added after the second paragraph of this chapter, i.e. before testing is considered in detail. **Proposed change:** The current text of the fourth paragraph should be implemented as third paragraph of Chapter 4.2.1.	**Comment accepted. This has been addressed in the revision.**
RBS 4.2.1. Cell line qualification,	It should be allowed the use the experience with a well established cell line with regard to cell line characterization. Therefore the sentence should be amended as proposed: **Proposed amendment of the text (new text is printed in italics):** 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 *can support cell line characterization and in specific cases* (e.g. data on susceptibility to a wide range of viruses) can contribute to the overall virus safety evaluation.	**Comment accepted. This has been addressed in the revision.**
PDA	The guidance draft requests testing of EOP cells “unless otherwise	**Comment accepted. This has been addressed in the revision.**

91	justified". However, the next sentence, implies that both WCB AND 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. 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. 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. "…When established, a WCB should be tested as outlined in Q5A**, chapter III A 2.**"	

	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.	
PDA 93	The requirement to test EOP cells grown at the "same scale" as used for the clinical batches contradicts with the requirements outlined in Q5A. For example Q5A states 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." .Growing EOP cellsat 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.	**Comment accepted. This has been addressed in the revision.**
PDA 95	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 *in vitro* cell age alone. 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.	**Comment accepted. This has been addressed in the revision.**
PDA 95	We have suggested revisions for the following language: *"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."* Suggest to revise as follows: Based on the risk assessment, it may be useful for manufacturers to examine cells taken beyond their in vitro	**Comment accepted. This has been addressed in the revision.**

	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.	
PDA 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."	**It was not felt that this guidance should be provided; however such reduced testing is provided for in unprocessed bulks, see 4.2.3.**
EFPIA/EBE (Cr) Section 4.2.1 paragraph 3 Line 85-86	*"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 requirement to use the 'same scale' as used for the clinical batches contradicts the requirements outlined in Q5A, where it is stated 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'. A risk based approach should be taken to the virus safety testing of EOP, taking into account the nature of the cell line and its susceptibility to harbouring infectious retroviruses as well 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 3. In this context we suggest that additional testing at the EOP cell level can be postponed for well characterized cell lines, for example CHO cells that have 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	**Comment accepted. This has been addressed in the revision.**

	lines such as NS0 cell lines we propose an appropriate testing regimen particularly focused at endogenous retroviruses. The term "cells at the limit of in vitro cell age" may be misinterpreted in a way that prolonged cultivation beyond production time is generally required. For clarity, only the term "*end of production (EOP) cells" should be used.* The following clarifying sentences should be added: "End of production (EOP) cells….should be derived from a minimum of one production batch representative of the intended clinical batch. For Phase 1, 2 and 3 study material, where well characterised cell lines are employed, the postponement of EOP testing can be justified by (i) testing MCB for endogenous and adventitious viruses; (ii) testing of the unprocessed bulk harvest of every batch for the absence of adventitious viruses; (iii) testing of at least one batch of unprocessed bulk harvest for retroviruses and retroviral particles; and (iv) validation of the virus removal capabilities of the process. For well-characterised cell lines, it is expected that EOP testing should begin in parallel with the initiation of Phase 3 clinical studies however it is not required for such data to be presented in the Clinical Trial Application."	
EFPIA/EBE (Ed) Section 4.2.1 Paragraph 3 Line 87	*"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 culture or purification processes may require a reassessment of the viral safety of the product and may entail partial or full re-assessment of the EOP cells".	**Comment accepted. This has been addressed in the revision.**
EFPIA/EBE (Ed) Section	There is no precedent or definition for the term "validated in house cell bank". However, ICH Q5D describes this same concept as a "characterized parental cell bank". Terminology should be aligned with	**Referral to a validated in house cell bank has been removed in the revision.**

4.2.1. Paragraph 5 Line 94	adopted ICH guidance documents. Replace “validated in-house cell bank” with “characterized parental cell bank”.	
EFPIA/EBE (Ed) Section 4.2.1. Paragraph 6 Line 97-101	This paragraph is considered generic and ambiguous, and further clarification is required. The guideline should be explicit regarding the acceptability of such replacement techniques. “Full validation” is not a defined concept in validation literature or in regulatory guidance. It is especially unclear in the context of the paragraph how the adjective “full” relates to cell-based assays and PCR assays. The validation achievable for each assay depends on the details of the science and technology, and the word “full” does not add useful information. Final sentence is outside of scope and should be deleted. If the sentence remains then the term “full validation” and “general acceptance” should be removed as it is ambiguous. ~~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.~~	**This statement has been fully revised/virtually deleted. The issue of qualification of analytical techniques is dealt with in section 4.2.5.**
Rentschler (Ed) Section 4.2.1.	*“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”*. Taking as an example well-characterised and widely used recombinant CHO cell line we do no see a significant increase in safety by testing EOP cells during various process development levels at clinical phase I/II. During development a certain number of process variations occur. For CHO cells derived from a well-characterised MCB and with a standard in-vitro cell culture assay for harvests it seems to be sufficient to evaluate the EOP virus status for phase III production and market scale (i.e. not necessary for earlier clinical development stages).	**Comment accepted. This has been addressed in the revision.**
4.2.2 UNPROCESSED BULK		
Line no. +	**Comment and Rationale**	**Outcome**

paragraph no.		
IMPG 4.2.2	i.e., at least three batches Change to i.e., three batches	**This has been taken onboard in revised 4.2.3**
RBS 4.2.2 Testing for viruses in unprocessed bulk	In this paragraph, the wording of the second sentence is not completely clear. The requirement to test at least three batches of unprocessed bulk material is related to the MAA and is not applicable to clinical material. It is therefore proposed to delete the text in brackets. **Proposed amendment of the text:** It is recognised that, early in clinical development, the number of batches that have been manufactured may be *limited*.	**This has been taken onboard in revised 4.2.3**
EFPIA/EBE (Ed) Section 4.2.2 Paragraph 1 Line 104	Per ICH Q5A, the method used to test for viruses in unprocessed bulk is not required to be quantitative. "Independent of the stage of development, the unprocessed bulk should be tested as defined in ICH Q5A including estimation ~~quantification~~ of retroviral particles…"	**Quantification of retroviral particles is necessary in order to be able to demonstrate adequate removal of them.**
EFPIA/EBE (Ed) Section 4.2.2 Paragraph 1 Line 103	The text in the draft guideline regarding number of batches could be misinterpreted and more explicit language is required. Since the number of lots manufactured early in clinical development may be limited, the wording "on at least a single lot of unprocessed bulk" should be added. "Independent of the stage of development, the unprocessed bulk should be tested as defined in ICH Q5A on at least a single lot of unprocessed bulk, where applicable."	**This has been taken onboard in revised 4.2.3**
4.2.3 VALIDATION (General)		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
IMPG Section 4.2.3 1st	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	**This is clarified in the revision.**

paragraph	data requirements for marketing authorisation". Further guidance is required as "full" validation at the end of Phase II is not likely.	
IMPG 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	**This is clarified in the revision.**
RBS 4.2.3. Validation of virus inactivation/removal	The term 'validation' is not used in the ICH Q5A guideline. In order to be consistent, this term should be replaced by 'evaluation'. **It is proposed to change the title of this Chapter to the following:** 4.2.3. Evaluation of virus inactivation/removal	**This is clarified in the revision.**
RBS 4.2.3. Validation of virus inactivation/removal	In general virus validation studies according to ICH Q5A are mostly not completed before phase III studies are performed. The request to finalize the studies before phase III would mean in such cases that phase III studies are postponed or phase III studies are performed before the final production and purification process has be established. Considering the current situation, the last sentence of the first paragraph should be amended by removing the statement that full virus validation according to ICH Q5A should be completed prior to phase III studies. It is not completely clear whether the term 'robustness' is really used in the sense of the ICH Q5A guideline. If so, this means that the investigation with different viruses in order to characterize the capacity of the process to remove/inactivate a broad range of viruses is not required. The proposed change is therefore only related to avoid the use of the word 'validation'. **It is proposed to delete the second part of the fourth sentence. This sentence should have the following wording:** Evaluation of virus inactivation/removal according to ICH Q5A should be initiated as soon as the final production and purification process has been established. **Proposed change in the first sentence of the second paragraph:** *Virus studies s*hould be performed according to the principles of Q5A although a demonstration of robustness may not be warranted at early	**Comment accepted. The guidance on this issue is completely revised.**

	stages of clinical development. …	
PDA 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."	**Comment accepted. The guidance on this issue is completely revised.**
EFPIA/EBE (Cr) Section 4.2.3 Line 117 Section 4.2.5 Line 181	*"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."* The default position in the draft guidance particularly with regard to expectations for Phase 3 is inappropriately restrictive, and is of significant concern to EFPIA & EBE members. Further elaboration of the guidance is required to define the data expectations for inclusion in the IMPD for a Phase 3 clinical study for different scenarios based on the risk/potential benefit assessment. It is agreed that <u>initiation</u> of viral evaluation studies according to Q5A should be initiated as soon as the final production and purification process has been established which could be before or in parallel with Phase 3 clinical studies. However <u>completion</u> of such studies is possible only once the final commercial process has been locked down and is typically accomplished in parallel with process qualification (PQ)	**Comment accepted. The guidance on this issue is completely revised.**

	and process validation (PV) of the commercial process. The Phase 3 manufacturing process is rarely identical to the Commercial manufacturing process; scale up, site transfers and process refinements are commonplace. The requirement for completion of studies to Q5A on the Phase 3 process as well as the commercial process would be extremely burdensome on Industry, resulting in significant delay to Phase 3 initiation, and the duplication of many studies. The rationale for the conduct of such studies prior to the initiation of Phase 3 clinical studies is contrary to the risk-based approach to assessment of viral safety advocated by other parts of the proposed guideline. Delete following text from Section 4.2.3<br ~~*"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."*~~ Section 4.2.5 should be deleted. Remit of Section 4.2.4 should be extended with the following text to include Phase 3 material. *"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 in parallel with the Phase 3 clinical programme for inclusion in the Marketing Authorisation Application, unless otherwise justified."*	
EFPIA/EBE (Maj) Section 4.2.3 Paragraph 2 Line 126	Reference is made to the CHMP note for guidance on virus validation studies (CPMP/BWP/268/95), which is applicable for commercial products, but it is not made clear to what extent this guideline is considered applicable to IMPs. In particular, 268/95 includes guidance on the interpretation of virus validation studies and defines the minimum level of clearance that a step must achieve before it can be considered effective (4 logs). However, for certain virus types (e.g. small non-enveloped viruses), it can be difficult to achieve this level of clearance for individual steps or the process overall. Whilst it is accepted that companies should take reasonable steps to ensure that the clearance capabilities of their processes are adequate for	**Reference to 268/95 remains pertinent as it describes the criteria for an effective step and notes that there is more to an effective step that the log no. of viruses removed. The revised guidance should clarify what is expected.**

	all virus types, it is felt that a rigid application of the LRF requirements stated in 268/95 is inappropriate for IMPs, particularly where the potential clinical benefits of trial participation outweigh the potential viral safety risk. It is recognised that, for IMPs where the purification process is still under development, the clearance of viral contamination to the levels expected for Commercial products (as defined in the CHMP Note for Guidance on virus validation studies) may not be achievable. In such scenarios, specific testing for viral contamination using Q-PCR or equivalent techniques, may be justified to mitigate the potential risk of viral contamination. The sponsor should justify within the context of the overall risk/benefit assessment.	
EFPIA/EBE (Ed) Section 4.2.3. Paragraph 2 Line 121	It should be clarified that per ICH Q5A, robustness is defined as "the capacity of the manufacturing process to remove and/or inactivate viruses in general" using "non-specific model viruses with differing properties". This definition should not be misconstrued to mean robustness as evaluated in process validation. Insert ICH Q5A definition of robustness or include a glossary to clarify terminology used in the guideline.	**The revision clarifies what is intended by a 'demonstration of robustness' in virus reduction studies.**
EFPIA/EBE (Ed) Section 4.2.3, Paragraph 2, Line 121	*''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	**This has been taken into consideration in the revised text.**

4.2.4 VALIDATION – PHASE I AND II

Line no. + paragraph no.	Comment and Rationale	Outcome
Merck Page 6 Line 9 (after 1rst	During very early development, edge-of-failure limits may not have been defined for new manufacturing processes. In these cases, use of representative (i.e. set-point) conditions is reasonable as long as the manufacturer can defend that the actual manufacturing process ran at	**Comment accepted; text revised accordingly, see 4.2.4.**

paragraph)	the set-points. Use of worst-case limits in the viral clearance study is relevant to platform processes and processes in late development, for which the level of experience is greater and edge-of-failure limits have been explored. "In performing the viral clearance/removal validation study, relevant levels process parameters should be used and defended (i.e. set points for new processes in early development, worst-case limits for platform processes and in late development)."	
Merck Page 6 2nd bullet point	The last sentence in the bullet point appears to represent a strong opinion. We suggest deleting the opinion, or adding a set of credible scientific references that support the point. Delete the last sentence, or add references.	**Point taken into consideration in the revision of the text regarding published data.**
Merck Page 6 3rd paragraph of 3rd bullet point	Much of this text is either extremely specific (i.e. regarding nanofilters) or extremely subjective ("If…is not entirely convincing…"). Consider rephrasing the concept for clarity. Limit 3rd paragraph of 3rd bullet point to the following with new text shown in red font: 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 for which in-house data will be applied.	**Point taken into consideration in the revision of the text.**
BIOGEN 4.2.4	Please confirm that "worse case" manufacturing parameters need not be proven experimentally, but rather based on a mechanistic understanding of and/or previous experience with similar inactivation/removal procedures. Experimental proof would require multiple studies to be performed with each virus for each new manufacturing process. Inclusion of statement confirming that "worse case" manufacturing parameters can be based on a mechanistic understanding of and/or previous experience with similar inactivation/removal procedures.	**Point taken into consideration in the revision of the text.**
BIOGEN 4.2.4	Please clarify, given the importance placed on retroviral clearance, whether it is acceptable to develop a generic claim for this virus type.	**Point noted in the revision of the text although it is not clear what is meant by a 'generic claim'.**

	Clarification regarding generic claims for retrovirus.	
BIOGEN 4.2.4	Section 4.2.4 states that "Two orthogonal steps should be assessed [for inactivation / removal of an enveloped virus] if possible". Please clarify whether the two orthogonal steps can be physicochemical and/or chromatographic. Can the the two steps can be confined to one of these clearance categories as long as differing mechanisms of actions apply. Definition of whether the two orthogonal steps can be physicochemical and/or chromatographic.	**What is meant by two orthogonal steps has been clarified.**
IMPG 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.	**Point taken into consideration in the revision of the text.**
IMPG 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"	**It is not felt necessary to expand on what is an enveloped virus.**
IMPG Section 4.2.4, second bullet	Published data should be used when applicable. Delete last sentence	**Point taken into consideration in the revision of the text.**
IMPG 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."	**It is felt that the original wording is clear and preferable.**
IMPG 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.	**This point has been taken onboard in the revision of the text.**

	Replace "if possible" with "where a single step is shown to be ineffective."	
IMPG 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).	**This point has been taken onboard in the revision of the text.**
IMPG 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."	**This point has been taken onboard in the revision of the text.**
IMPG Section 4.2.4 paragraph 4 bullet 3 sub	*''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''.*	**This point has been taken into consideration in the revision of the text.**

paragraph 3 sentence 1	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.	
IMPG 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."	**Reference to the requirements for the MAA has been avoided in the revision.**
RBS 4.2.4. Validation of materials for Phase I and II studies	It is proposed that the next three Chapters (currently 4.2.4 and 4.2.5 as well as a new Chapter containing a part of current Chapter 4.2.4) should be subchapters of 4.2.3. Change of the titles is proposed to avoid confusion in the use of the term 'validation' **Proposed change in structure and titles:** **4.2.3. Evaluation of virus inactivation/removal** **4.2.3.1. Evaluation of materials for Phase I and II studies** **4.2.3.2. Evaluation of materials for Phase III studies** **4.2.3.3. Circumstances for a reduced program of virus clearance studies**	**The revised text has new structure of chapters and the term validation has been avoided.**
RBS 4.2.4. Validation of materials for Phase I and II studies	It is proposed to use the correct terms 'retrovirus' and 'retrovirus like particles' and to avoid the term 'validation'. **The current text should be amended to the following:** Case B cells (as defined in ICH Q5A) contain *endogenous retroviruses or retrovirus like particles* and a retrovirus should be used in *evaluating* the inactivation/removal of viruses to demonstrate full clearance of particles present in the bulk harvest.	**This point has been taken onboard in the revision of the text.**
RBS	In the third paragraph it is proposed to use the limits of process	**This point has been taken onboard in the revision of the text.**

4.2.4. Validation of materials for Phase I and II studies	parameters for performing virus studies. This is good but the text should not imply that this reflects 'worst-case conditions'. It is sometimes not to predict what worst-case conditions are. In very early stages of development the limits of process parameters might not yet been defined so that the target values have to be considered. The manufacturer should justify the approach taken but it is proposed to delete the text in brackets. **It is proposed to delete the text in brackets and read the sentence as following:** In performing virus clearance studies, the limits of process parameters should be used, if not otherwise justified.	
RBS 4.2.4. Validation of materials for Phase I and II studies	It is stated already in Chapter 4.1 that 'in-house experience may also be applicable to the data requirements of an MAA'. It should be considered therefore to allow the use of in-house data for clinical material in later stage of development. If so, it would be better to re-locate this complete part as an additional Chapter: **The text should be amended as following:** The third paragraph should be deleted and re-located as Chapter *4.2.3.3. Circumstances for a reduced program of virus validation studies* The fourth paragraph should be maintained in this chapter as the third paragraph: Due to the use of dedicated columns and the comparability …. they will be expected in the MAA.	**Reference to data requirements for the MAA has been deleted.**
RBS 4.2.4. Validation of materials for Phase I and II studies	The part describing the conditions for a reduced program for virus clearance studies should become a separate chapter (4.2.3.3.). In the last paragraph, line 5, the term 'nanofilter' is used. It should be replaced by 'virus filter'. The term 'virus filter' or 'virus retention filter' is more appropriate as it relates directly to the case that filter have been developed for this application whereas the term 'nanofiltration' is used also for other applications (e.g. water purification). **The term 'nanofilter' should be replaced by the term 'virus filter'.**	**This has been given a separate sub-section.** **The term 'nanofilter' has been avoided.**
PDA 123	It is important to clarify that full validation according to Q5A would not include resin reuse studies. This is is acknowledged in section 4.2.4 last paragraph as not needed for investigational material, but would be	**This point has been taken onboard in the revision of the text; reference to MAA requirements has been omitted.**

	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	
PDA 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	**The term is used loosely and does not require a definition.**
PDA 151	*‘’Two orthogonal steps should be assessed, if possible’’*. For small, non-enveloped virus inactivation/removal, it is often feasible to demonstrate the robustness of only one effective process step early 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. 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" Replace "if possible" with "where a single step is shown to be ineffective."	**These points have been taken onboard in the revision of the text.**
PDA 152	We have limited knowledge of the “worst case parameters” for viral removal. It is inappropriate to assume that the worst case parameters	**This point has been taken onboard in the revision of the text.**

	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. 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)	
PDA 158	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. 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. 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. Delete last sentence of this paragraph.	**This point has been taken onboard in the revision of the text.**
PDA 178	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 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	**The guidance provided in referring to "purified by identical methods" is felt to be adequate and appropriate.**

	identical unit operations Replace "purified by identical methods" with "purified by identical methods and/or methods with similar process performance parameters, as justified".	
PDA 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.	**This point has been taken onboard in the revision of the text.**
EFPIA/EBE (Maj) Section 4.2.4 Paragraph 2 Line 140	*''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 with: "Two orthogonal steps should be assessed, where a single step is shown to be ineffective."	**This point has been taken into consideration in the revision of the text.**
EFPIA/EBE (Ed) Section 4.2.4 Line 128	Title should be made more explicit. Also applies to the title of 4.2.5. It seems that Sections 4.2.4, 4.2.5 and 4.2.6 should be subsections of Section 4.2.3 rather than Sections in their own right. Change to: "Validation of virus inactivation / removal for Phase I and II studies"	**The layout of sections and their titles have been revised.**
EFPIA/EBE (Ed) Section 4.2.4 Paragraph 1 Line 132	The term "full clearance" is misleading as it implies 100% removal of virus particles. Viral inactivation procedures may result in non-viable particles, which could still be detected by PCR testing. Alternatively, a residual number of intact, viable virus particles may be lower than the limit of detection for cell based assays. Replace "full clearance" with "adequate clearance" or "sufficient clearance".	**It is felt that the term 'full clearance' provides appropriate guidance without spelling out these finer points. The use of terms such as 'adequate' and 'sufficient' always beg the question as to what is adequate/sufficient.**
EFPIA/EBE	If the MCB is a Case B in ICH Q5A (such as a CHO cell) Phase I	**This has not been taken onboard in the revision in order to maintain**

(Ed) Section 4.2.4 Paragraph 1 Line 137	clinical trial studies should be permitted to commence as a long as a solvent/detergent or detergent step is used in the process. Considerable flexibility should be given to not generating new viral clearance data as outlined in 4.2.4. The following should replace the first sentences Consequently, prior to the initiation of 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. Justification includes use of a solvent/detergent or detergent step in the process.	**a broad emphasis on all virus and cell types from the very start of clinical development.**
EFPIA/EBE (Ed) Section 4.2.4 Paragraph 3 Line 141	*''In performing the evaluation 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 may not 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 with: ''In performing the evaluation study, target process parameters should be used. It may be advisable to use worst-case conditions as they apply to viral clearance where applicable (e.g. usage of the highest pH realised in the manufacturing process for virus inactivation)"	**This comment has been taken onboard in the revision.**
EFPIA/EBE (Ed) Section 4.2.4 paragraph 4 bullet 2 Line 145	*''Published data are especially unreliable where the removal of viruses is virus specific or not predictive in general.''* We agree with the draft document on limited use of published data to support modular viral validation. Published data usually do not provide sufficient information on all of the process parameters for a unit operation. These 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	**This comment has been taken onboard in the revision.**

	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.”	
EFPIA/EBE (Ed) Section 4.2.4 paragraph 4 Line 162	*’’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 operations can provide data to define acceptable conditions for viral inactivation / removal. Replace "purified by identical methods” with “purified by identical methods and/or similar process operational parameters”.	**The guidance provided in referring to "purified by identical methods” is felt to be adequate and appropriate.**
EFPIA/EBE (Ed) Section 4.2.4 Paragraph 5 Line 177-179	It should be noted that resins are dedicated to a specific product and columns may be shared between products. It is assumed from the text that this also includes phase III material, such studies are generally not required for the same reasons as described above but will be required for the MAA. Final sentence should be deleted, out of scope. Due to the use of dedicated chromatographic resins and the comparably small number of batches manufactured during clinical 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.~~	**This comment has been taken onboard in the revision.**
4.2.5 VALIDATION – PHASE III		

Line no. + paragraph no.	Comment and Rationale	Outcome
EGA 4.2.5	There is perhaps an area of potential uncertainty in this section on phase III trials which refers to Q5A, because it does not really clarify how and why any differences in methodology with an approved product should be different compared with an IMP for a phase III study, and what could be used for justification of any differences.	**This issue has been addressed with revised guidance.**
IMPG 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."	**This issue has been addressed with revised guidance.**
IMPG 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."	**This issue has been addressed with revised guidance.**
RBS 4.2.5. Validation of materials for Phase III studies	Change of the wording from 'validation' to 'evaluation' and provide this chapter as sub-chapter 4.2.3.2. 4.2.3.2. Evaluation of virus inactivation/removal for Phase III material	**This comment has been taken onboard in the revision.**
RBS 4.2.5. Validation of	If it is accepted that the final production and purification process might not be defined prior to phase III studies, the full validation according to ICH Q5A should not be required before phase III studies are initiated.	**This issue has been taken onboard in the revised guidance.**

materials for Phase III studies	This implies however, that the requirements for phase III materials are defined. The proposed wording should be seen as an attempt to differentiate between requirements for clinical material and requirements for the MAA. In the interest of harmonised requirements for the virus safety assessment of clinical materials it would be valuable to express clearly in this paragraph whether sanitization studies are needed if columns are re-used in this stage of development and whether studies are expected demonstrating virus partitioning on re-used columns in relation to virus partitioning on new resins. According to the current experience that virus partitioning on new or re-used resins may very only in extreme cases, it is proposed to require the investigation of the sanitization procedure before phase III studies are initiated if column recycling is performed. This request may be beneficial for the manufacturer as well as it may demonstrate that there are limitations which require a change in the procedure or regeneration and sanitization using higher volumes to wash and purify (high salt wash) the resin before re-use. **Proposed change of the text for this paragraph:** *Evaluation of virus clearance according to ICH Q5A should be initiated as soon as the final production and purification process has been established*. Prior to Phase III studies it must be demonstrated that that there is excess capacity for virus clearance built into the purification process to assure an appropriate level of safety for the final product. The data generated for clinical material in earlier stages of development may be used but changes in manufacturing conditions during development that may influence directly or indirectly (by changes in other then the evaluated manufacturing stages) the virus inactivation/removal capacity of the process must be considered; re-evaluation might be needed. The selection of viruses should be reconsidered and additional viruses implemented if needed to provide confidence in the capacity of the process for robust clearance of viruses. Even if not a complete evaluation of the process capacity for virus inactivation/removal according to ICH Q5A is required, manufacturers should justify the approach taken, considering the model viruses used and the number of steps involved in the evaluation of the process. The investigation of potential effects of variation in process parameters on virus inactivation/removal are generally not required for Phase III	

	material but should be considered in the discussion of the virus clearance data; they will be expected in the MAA. If columns are re-used in this stage of development, sanitization studies should be performed to demonstrate its effectiveness for virus inactivation; due to the small number of column recycling for clinical material studies demonstrating virus partitioning on re-used columns vs. new columns are generally not required for phase III material. However, data will be expected in the MAA.	
PDA Page 7, section 4.2.5	Issue 1: The expectations of the draft document will unnecessarily increase product development timelines by postponing the start of Phase III. 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 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.	**This issue has been taken onboard in the revised guidance.**
PDA Page 7, section 4.2.5	**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: 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 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.	**This issue has been taken onboard in the revised guidance.**

	Examples: • 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.	
PDA Page 7, section 4.2.5	**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. 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. 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.	**This issue has been taken onboard in the revised guidance.**
PDA Page 7, section 4.2.5	Issue 4: Economic considerations can impact whether a product proceeds in the development pipeline. 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.	**This issue has been taken onboard in the revised guidance.**

PDA Page 7, section 4.2.5	**Issue 5**: The current safety record of biopharmaceuticals are excellent. 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.	**This issue has been taken onboard in the revised guidance.**
PDA Page 7, section 4.2.5	**Issue 6**: The safety approach for biopharmaceuticals is multi-faceted and robust. 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.	**This issue has been taken onboard in the revised guidance.**
PDA 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.”	**This issue has been taken onboard in the revised guidance.**

4.2.6 VALIDATION ANALYTICAL TECHNIQUES		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
MERCK Page 7 Sec 4.2.6	It is not clear if this section applies only to the quantitative tests used in the viral inactivation/removal validation study, or if it applies to the various viral "limit" tests used as part of the qualification of the cell banks prior to Phase I studies. The validation parameters appropriate for a limit test are quite different than those for a quantitative test. Note also that no viral tests are actually described in the EP in detail such as that provided for mycoplasma or sterility testing, for which it is accepted that revalidation is unnecessary (only "qualification" of new test articles). Please clarify.	**This comment has been taken onboard in the revision.**
MERCK Page 7 Sec 4.2.6	This sentence is quite unclear: "Viral tests performed in accordance with the European Pharmacopoeia are normally not (re-) validated by the company." Since the EP does not actually describe the viral tests in detail for biologics as it does for others like mycoplasma and sterility, does this mean that all viral "limit" tests need to be validated, or does it mean that scientifically suitable viral limit tests, such as those mentioned (but not described) in the EP do not need to be validated? Please clarify scope of this section.	**This comment has been taken onboard in the revision.**
EGA 4.2.6 para 2	The guideline states "Viral tests performed in accordance with the European Pharmacopeia are normally not (re-)validated by the company". EGA comments: There are currently no compendial methods for analytical procedures applicable to biotechnological products specific for viruses, comparable to those that have been published for e.g. mycoplasma testing. (There is only a chapter on virus testing technical details for vaccines) We would like to emphasise that it is very desirable to have compendial methods for virus testing for several reasons: 1. A very important part of validation of tests for viral contamination is the detection limit for specific viruses. For this kind of validation, reference standards are needed, e.g. virus stocks with a	**This comment has been taken onboard in the revision.**

	defined virus concentration. The determined virus concentration of a virus stock is highly dependent on cultivation conditions and indicator cell line used for quantification. Therefore, different testing sites use virus stocks as reference standards for validation and as positive controls which may not necessarily be comparable. Guidance from authorities (for example via compendial methods) on how to prepare reference standards for virus stocks would allow standardization of the most common virus test methods. 2. Clear guidance (for example via compendial methods) would be very helpful to define the requirement of sample-matrix specific validation of tests for viral contamination, e.g. spiking of sample with positive control to determine interference (as it is described for example for compendial Mycoplasma testing). Such validation is currently not common for tests for viral contamination. For phase I/II clinical trials, such sample specific validation should not be required. 3. Guidance from authorities (for example via compendial methods), on which viruses should be included in such validation studies for the most common virus test methods (e.g. in vitro assay, electron microscopy) would be appreciated. 4. It should be noted that in vivo test methods for viral contamination usually are not validated. Validation would mean a torture and death for a lot of animals, especially since very many viruses could be validated in such studies. If validation is recommended, these studies should be done once and then a compendial method should be described which avoids further validation studies by the individual test sites. 5. In general, several virus test methods are currently not or not fully validated by some contractor test laboratories. Before coming into force, 6-12 months for implementation of the new guidance should therefore be considered to allow sufficient time for validation of the methods.	
IMPG 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.	**This comment has been taken onboard in the revision.**

RBS 4.2.6 Validation of analytical procedures	The requirements of this chapter are not clear. The request for validation of analytical procedures is part of the general provision of production of IMPs according to the principles of GMP (Directive 2001/20/EC and Annex 13 GMP). Viral tests apart from PCR assays validation are not directly implemented in the methodology provided by Ph.Eur. or are laid down for the control of vaccines (e.g. 2.6.16). No requirements related to analytical procedures are implemented in ICH Q5A. The meaning of the requirements implemented in this Chapter is therefore not clear. If it is the intention to require here that sufficient sensitive methods should be used for detection of retrovirus and adventitious viruses in MCB and EOP/unprocessed bulk or that sufficient sensitive methods for virus detection should be used when virus clearance studies are executed, this might be covered by the reference to the ICH Q5A guideline or should be clearly stated in this Chapter. The requirements given by this Chapter should be clarified. **It is proposed to clarify the meaning of the requirements laid down in this Chapter or, if the requirements are covered by other documents, e.g. ICH Q5A or GMP regulations, it is proposed to delete the Chapter 4.2.6. Validation of Analytical Procedures.**	**This comment has been taken onboard in the revision.**
PDA 206	Regarding the sentence: *"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."* . 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 . . ."	**This comment has been taken onboard in the revision.**
EFPIA/EBE (Maj) Section 4.2.6 Line 184	Consistent with the requirements of CHMP/QWP/185401/2004 (Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials), it should not be necessary to provide full validation reports for analytical procedures. Furthermore, consistent with ICH Q5A, "assays should include	**This comment has been taken onboard in the revision.**

	appropriate controls to ensure adequate sensitivity and specificity." Analytical methods employed are not validated, but rather qualified. Formal analytical validation studies for methods applied for viral testing may not be performed on a product by product basis and are usually qualified to reflect the nature of the method used. There is no distinction based on the phase of development. Revise as follows: 4.2.6 ~~Validation~~ Qualification of Analytical Procedures "~~For Phase I/II clinical trials,~~ The suitability of the analytical methods applied for viral testing should be stated and demonstrated in a tabular summary, as appropriate. A tabulated summary of the results of the qualification, carried out according to ICH methodology, should be provided ~~(e.g. results of values found for the specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate).~~ Assays should include appropriate controls to ensure adequate sensitivity and specificity. Viral tests performed in accordance with the European Pharmacopoeia are normally not (re-) qualified 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 RISK ASSESSMENT		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
IMPG 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''*	**These comments have been taken onboard in the revision.**

	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.	
IMPG 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.	**This comment has been taken onboard in the revision.**
RBS 4.3. Virus safety risk assessment	The last sentence of the first paragraph might be misleading when it is read as an argument for less or higher virus safety requirements for products applied to patients who might or might not be immune against infection with specific viruses. The meaning of this statement should be clarified. **Proposed change:** The meaning of the sentence 'It should be noted that the immunological status of the phase II and phase III trial group may differ form those in the phase I group' should be clarified.	**This comment has been taken onboard in the revision.**
PDA 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.	**"Raw" has been deleted.**
PDA	Regarding the sentence: *''[…] a risk assessment should be provided*	**This has been clarified.**

211	*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.''* 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).	
MHRA	In section 4.3 the following sentence appears: ' 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 purpose of the phrase is a little opaque unless it is understood that phase I subjects are healthy volunteers.	**This has been taken onboard in the revision.**
EFPIA/EBE (Ed) Section 4.3, Paragraph 1 Line 198	*''[…] 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	**This has been clarified.**
EFPIA/EBE (Ed) Section 4.3 Paragraph 1 Line 200	*"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 "quality related" aspects. Clinical parameters, such as dosing, patient	**These comments have been taken onboard in the revision.**

	number, study duration, should not be the primary decision basis for the viral safety risk assessment. However the inclusion of such criteria as part of a justification to mitigate sub-optimal clearance levels, or to postpone the conduct of certain studies to later stages of development, is supported. The guideline requires to give an assessment of the immune status of the patients, in order 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 phases of development. In case of patient with weaker immune status, the probability of contamination by a virus of the environment is higher 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 such parameters may change between Phase I, II and III. Additional clinical parameters may be of value and may be included in the risk assessment if applicable"	
4.4 RE-EVALUATION DURING DEVELOPMENT		
Line no. +	**Comment and Rationale**	**Outcome**

paragraph no.		
IMPG 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."	**This has been taken onboard in the revision.**
IMPG 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".	**It was not felt necessary to provide such examples. The revised text provides guidance on how manufacturers should manage changes.**
IMPG Section 4.4 last paragraph	Not applicable. Delete last paragraph	**Noted and taken onboard in the revision.**

4.5 DOCUMENTATION		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
MERCK Page 8 Sec 4.5	At least 2 documents are cited in this section, but which appear not to be included in the reference list (III/5512/93). Please include all references in the list.	**This has been corrected.**
IMPG 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.	**Point noted but references useful.** **Reference added.**

IMPG 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?	**Comments noted and taken into consideration in the revision.**
IMPG 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.	**This comment has been taken into consideration in the revision; however expansion of the guidance by providing such examples was not felt to be appropriate.**
RBS 4.5. Format of clinical trial authorization documentation.	In the second paragraph, the format of reporting should consider the nomenclature in the IMPD: Attachment 2 is 2.1.A.2. The wording should be amended. In this paragraph, the term 'generic data' is used. In order to be consistent in this document, the term 'generic data' should be replaced by the term 'in-house data'. It is not completely clear what does it mean if it is required: 'The level of detail should be adapted to the stage of development'. Full reports and raw data might be required also for clinical material for phase I/II studies. Such a request would not require extra work from the sponsor because the reports must be available if the data are reported;	**Points taken onboard in the revision.**

	furthermore, it should be made clear for the sponsor that raw data are required and should be provided by contract laboratories or internal labs as part of the reports. The extent of data is different between the stages of development but this does not implement that the level of reporting is different. It is proposed to clarify this request or to delete this sentence (see proposal). The request of full reports and raw data should be clarified (see the proposed amendment). **For the second paragraph of the chapter the following wording is proposed (changes are printed in bold):** 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: **2.1.**A Appendices, **2.1.**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. It should be noted that **full reports including raw data of cell line testing and virus clearance studies** might be required. When the applicant makes use of **in-house** data (i.e. data from other products), an adequate package of data should be provided to allow an assessment of the **in-house** data and to provide confidence that these data are valid or supportive for the specific product under development.	
PDA 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. 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	**This comment has been taken into consideration in the revision; however expansion of the guidance by providing such examples was not felt to be appropriate.**

	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. 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?	
EFPIA/EBE (Ed) Section 4.5	Numbering of attachments should be corrected. It is mentioned that the section should be self-standing/ without other sections to be consulted. However, the section should be comprehensive enough to be able to evaluate the virus safety of DS and DP and references to other relevant sections (e.g. S.2, S.4 should be allowed without repetition of information. The sentence "*It should be noted that raw or…*" has no edit value, instead it might allow most diverse interpretation from different health authorities. Cross reference to guidelines intended for commercial products may lead to inappropriate expectations for different Member States. "Complete and detailed documentation" for raw materials of biological origin is ambigious and should be deleted or clarified. 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: 2.1 ~~3.2.~~A Appendices, 2.1 ~~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~~	**These comments have been taken into consideration in the revision.**

	~~Attachment in order to be self-standing and understood in its entirety without other sections of the main dossier having to be consulted.~~ The section should be comprehensive and detailed enough to support an assessment of the virus safety of the IMP. References to other relevant sections should be utilised to avoid a repetition of information. 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 by the document on "Contribution to part II of the structure of the dossier for applications for marketing authorisation Commission of the European Communities III/5512/93".~~ ~~Particular attention should be paid to raw material of biological origin for which a complete and detailed documentation should be provided.~~	
EFPIA/EBE (Ed) Section 4.5 Line 223	The guidance on the format of viral safety information in the IMPD is helpful, as it will further promote harmonisation of expectations amongst the member states regarding the content and format of the dossier. In light of this detailed guidance, it is considered that there should no longer be any requirement to provide viral safety information in formats other than the IMPD. In this respect, we propose that the viral safety form currently required for applications in France is withdrawn.	**This comment has not been taken onboard in the revision. It is inappropriate for the guidance to cover this.**
EFPIA/EBE (Ed) Section 4.5 Line 232	*"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."* Delete sentence or further elaborate circumstances which may justify provision of raw data / full reports, and at which stage(s) of development.	**This comment has been taken into consideration in the revision; however expansion of the guidance by providing such examples was not felt to be appropriate.**
MHRA	Section 4.5 provided some concern as to the level of data expected to be provided. This section suggests that raw data or full reports might be required, but no indication is made of the circumstances when this would be applicable.	**This comment has been taken into consideration in the revision; however expansion of the guidance by providing such examples was not felt to be appropriate.**