14 September 2011
EMA/360578/2010
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on Guideline on plasma-derived medicinal products EMA/CHMP/BWP/706271/2010 (formerly CPMP/BWP/269/95 rev. 3)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	PPTA - Plasma Protein Therapeutics Association
2	IPFA - International Plasma Fractionation Association
3	Sanquin Plasma Products, Amsterdam, The Netherlands
4	Dr. Albrecht Gröner, CSL Behring, Marburg

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	Proposed changes: Replace parvovirus B19 (and not B19 virus) and use the ICTV abbreviation B19V, use the term virus filtration and not nanofiltration.	The comment is accepted. The wording is changed throughout the document.
2	There are quite a few typographic errors (not detailed here), and in a few cases words seem missing: e.g. line 164: "… medicinal product is granted, the manufacturer…" and line 852: "… and realistic worst case scenarios should be considered in order to…" The nomenclature for parvovirus B19 is not used consistently throughout the text. We suggest the guideline include the monograph numbers in Annex II	The typographic errors have been corrected. B19V nomenclature has been harmonised throughout the text. Monograph numbers will be included in Annex II.
4	Virus safety, virus reduction etc., I prefer the substantive virus instead of the adjective viral as (my usual example) a high safety is not safety from altitude. Furthermore, if the more general term pathogen safety is (would be) used, nobody would say pathogenic safety etc. Term nanofiltration should be replaced by virusfiltration (that is what I learned from different sources, e.g. PDA, as the term nanofiltration is taken by the nanoparticle people) Parvovirus B19 should be used (not any longer B19 virus) with the appropriate abbreviation B19V (and that B19V is not an example of a very resistant small non-enveloped virus (this topic will be addressed in detail by PPTA))	The term “virus safety” has been considered throughout the document. The term nanofiltration has been replaced by virus filtration where appropriate, however, because nanofiltration is a well know term for this step it should be explained, e.g. virus filtration (also know as nanofiltration) Nomenclature of B19V has been harmonised.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
160	2	**Comments:** Should be specified that it applies to Product used in EU **Proposed change:** To add at the end of the sentence "medicinal products used in EU "	Further guidance for plasma for fractionation from third countries and for third country contract fractionation is provided in the revised GMP Annex 14 coming into effect 30 November 2011.
161 - 162	1	**Proposed change:** Add the underlined to the sentence: “These requirements refer, where applicable, also to blood/plasma and plasma-derived medicinal products imported from third countries, if finished product is intended for marketing and distribution within the EU.”	See above.
162	2	**Comments:** Should be specified that it applies to Product used in EU **Proposed change:** To add at the end of the sentence "imported from third countries and used in EU".	See above.
170 - 174	1	**Comments:** This is not a solid statement and the example is not relevant. There are more serious differences than retention samples as not considering cold ethanol fractionation.	Not accepted. The comment is not clear. However, text has been modified to make reference to the provisions of the Treaty on the Functioning of the EU and to address separately requirements for Official Control Authority Batch Release.

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		Proposed change: Delete.	
185	2	**Comments:** Line 185-188 requests that the PMF annual update be approved. Is approval via a variation procedure? Any information that is not covered by the annual update is submitted and approved through variation applications. If the annual update is now going via the same route should it not be redefined as an annual update variation?	Annual update is not a variation although variations can be submitted at the same time. For clarification it is added: a) After line 184: All information on the starting material should be in accordance with the Guideline on the scientific data requirements for a plasma master file (EMEA/CHMP/BWP/3794/03). It may be provided as a PMF. b) In line 186: If a MAH decides not to use the PMF certification procedures, it is also possible to provide the same information in Module 3, section 3.2.S. of the documentation for the medicinal product. The PMF or the plasma documentation in Module 3, section 3.2.S This information should be updated and re-submitted for approval on an annual basis. Reference to more than one PMF is possible and should be clearly indicated in the dossier.
208	2	**Comments:** To reassure patients who use plasma derived products, it should be stated that preventive measures are already required. **Proposed change:** In addition any contaminating virus is able by definition to infect humans in the absence of any preventive measures.	Not accepted. This is the wrong place to talk about measures already in place because this section states the risks. In order to not worry patients unnecessarily the sentence: “In addition any contaminating virus is able by definition to infect humans.” in line 207/208 has been deleted.
218	2	**Comments:**	Accepted.

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		There is scope to clarify and reiterate the requirements of directives relating to imported plasma. Line 218/219 states that the donors should be in compliance with Directive 2202/98/EC and 2004/33/EC. To be grammatically accurate the statement should be that selection and exclusion criteria should be in compliance with Directive 2202/98/EC and 2004/33/EC. However this statement makes no mention of how these directives are to be applied to imported material. Directive 2002/98/EC makes clear requirements for national control of blood establishment licensing and control at national level. It also lays down specific requirements for imported components at item 17, p 31, Article 14, 1 & 2Article 21Likewise Directive 2004/63/EC makes specific requirements for imported plasma that it should meet "the quality and safety requirements set out in this directive". Those requirements are defined in Article 6 as being listed in Annex V. Therefore the Directives do require that imported plasma must meet the exact requirements of 2004/33/EC Annex III. Although the Directive 2002/98/EC quotes the Council recommendation 98/463/EC in OJ L 203, 21.7.1998,p14 http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:203:0014:0026:EN:PDF where numerous of the deferral criteria are for the safety of the donor the proposed 269/95 draft does not	Line 218/219: The comment is accepted. The wording has been revised: “Selection and exclusion criteria for blood/plasma donors should be in compliance with Directive 2002/98/EC and 2004/33/EC.” Further guidance on the applicability of these Directives for plasma for fractionation imported from third counties is provided in the revised GMP Annex 14 coming into effect 30 November 2011.

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		make it clear that donor exclusion for donor safety in third countries is a matter for the third country. It also does not allow for the Council recommendation that the standards must take into account existing standards at the national level (item 20, p15). A good example of the current confusion is the differences in haemoglobin limits between the US and EU. **Proposed change:** It is suggested that 269/95 should clarify the position that 2202/98/EC and 2004/33/EC make specific requirements for imported plasma only and other donor deferral and screening procedures may provide an equivalent level of safety and quality.	
231	2	**Comments:** Why are the anti-D immunoglobulin monographs specifically mentioned? They are not applicable for each donation and plasma pool.	Accepted. The comment is accepted and the wording revised as follows: Each donation should be tested in compliance with Directive 2002/98/EC, Directive 2004/33/EC and the Ph. Eur. monograph “Human plasma for fractionation”. Plasma pools should also be tested according to the monograph “human plasma for fractionation”. Additional testing and specifications of plasma pools are required for specific products, e.g. virus inactivated pooled plasma and anti-D immunoglobulins. If normal immunoglobulin for intramuscular/intravenous administration and/or albumin are used in the manufacture of anti-D immunoglobulin, the plasma pools from which they are

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			derived should comply with the requirement of the respective Ph. Eur. monograph on anti-D immunoglobulin
232 - 233	1	**Comments:** Citation of the guideline is not applicable. The PMF gives no guidance for required testing. This is stipulated by other regulations. **Proposed change:** Delete.	The comment is acknowledged. The wording is revised to quote the PMF guideline with respect to validation: "For validation of all testing methods, reference is made to the Guideline on scientific data requirements for a Plasma Master File (EMEA/CHMP/BWP3794/03)."
237	2	**Comments:** Line 237-249 discusses the need for B19 NAT and bases the limit on the virus reduction capacity of the manufacturing process. In the light of limits for B19 being discussed by the FDA we would propose that EMEA consider harmonising their approach to this virus with the opinions of the FDA?	Harmonisation with FDA requirements would mean to introduce a B19V limit of 104 IU/ml for plasma pools. This has been discussed by the drafting group, BWP and BPWP. There is agreement between European experts to support a case-by-case evaluation as currently described in the guideline: "B19V has been transmitted by plasma-derived medicinal products such as coagulation factors, fibrin sealants, and by solvent-detergent treated plasma. In immuno-competent patients without specific underlying diseases, the infection is usually asymptomatic or mild. However, transient aplastic crisis may be observed in patients with erythropoietic disorders while prolonged anaemia may occur in immuno-compromised patients. Highly viraemic donations occur quite frequently and may lead to high contamination levels of plasma pools with more than 10^8 IU/ml of B19V DNA. It is recognised that NAT screening for exclusion of such high titre donations can significantly reduce the contamination of plasma pools thereby reducing the risk for transmissions and resulting potential complications. Therefore, introduction of high titre screening is

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			encouraged. The appropriate limit for contamination of plasma pools depends on the B19V-reducing capacity of the product-specific manufacturing process. A risk assessment according to chapter 9 of this guideline is performed in order to substantiate claims that a product can be considered safe with respect to B19V infection." The lines 251 to 257 provide redundant information and have been deleted.
243	2	**Comments:** Official abbreviation for millilitres is ml and not mL. **Proposed change:** Highly viraemic donations occur quite frequently and may lead to high contamination levels of plasma pools with more than 10 IU B19 DNA per ml.	Accepted. "mL" has been changed to ml.
247	1	**Comments:** "A risk factor according to chapter 4.6 of this guideline…." Chapter 4.6 does not exist in this document.	The comment is acknowledged. Reference is made to chapter 9 of this guideline.
267 – 275	1	**Comments:** According to Directives 2002/98/EC and 2005/61/EC the 30 year archiving is only applicable for "blood components" (i.e. as per definition in Directive 2002/98/EC: "Therapeutic constituents of blood") for the process from the single donation to the transfused recipient identification or confirmation of subsequent	This section does not concern documentation retention requirements for finished products. It addresses the requirements for keeping the link from a donation/donor to the finished product. This information needs to be kept for 30 years. Annex 14 GMP makes the following statement: "Data needed for full traceability must be stored for at least 30 years, according to Article 4 of Directive 2005/61/EC and

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		disposition. As stipulated in Directive 2005/61/EC documents for traceability through the entire manufacturing process at the fractionator do not have to be archived for 30 years. Currently such documents for traceability through the fractionation process are only kept for one year beyond expiration date of the final product. **Proposed change:** The document retention requirement for therapeutic products derived from human blood or plasma derived ("blood products" as per definition in Directive 2002/98/EC) should be kept as for any licensed medicinal product for one year beyond expiration date of the final product.	Article 14 of Directive 2002/98/EC." For clarification the wording is revised as follows: "To ensure that the duration of traceability is not shorter for batches of medicinal products compared to their raw/starting materials, a link from donation/donor to finished product should be maintained by the manufacturer of the plasma-derived product for at least 30 years after the time of the donation (see GMP Annex 14)."
272	2	**Comments:** Line 272 requires traceability records to be kept for 30 years. Although this is in the Blood Directive this seems excessive. Is there a scientific basis for the choice of 30 year records?	See above.
277 - 281	1	**Comments:** According to the Directives 2002/98/EC, 2005/61/EC and 2005/62/EC, Reporting of serious adverse reactions is applicable for blood and blood components, but not for plasma for fractionation in this context. Therefore, we recommend changing Lines 277 - 281 as described above	The proposed change is not accepted. If a serious adverse reaction from transfusion of a blood component implicates plasma from the same donation, then reporting is applicable.

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		Proposed change: A post collection information system should be in place describing the measures for reporting of serious adverse events.	
278	2	**Comments:** Chapter 4.4 refers to starting material. As sentence line 277/278 is written, it may be understood that the adverse reactions and events relate to a pharmacovigilance issue. For clarification we propose to add at the end of the sentence "in donors or related blood product recipients". **Proposed change:** A post collection information system should be in place describing the measures for reporting serious adverse reactions and events in donors or related blood product recipients.	Partly accepted. Wording of the first paragraph has been revised to improve clarity.
287 - 288	2	**Comments:** Could you confirm that PMF Holder means holder of a certified PMF? **Proposed change:** "If the reliability of a blood establishment/centre or the quality and safety of plasma could be questionable the holder of a certified PMF should inform …".	PMF Holder (PMF-H)" means holder of a certified PMF. This term is used in analogy to a marketing authorisation holder (MAH). In case no certified PMF is available the term used for the person seeking certification of a PMF is "Applicant"
286 - 288	1	**Comments:**	Not accepted.

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		PMF Holder should inform national competent authorities and EMEA only if the quality and safety of plasma is endangered. **Proposed change:** If the quality and safety of plasma is endangered the PMF holder should inform national competent authorities and the EMEA as the PMF certification body.	The competent Authority should also be informed if the reliability of a blood establishment is questionable. No change is deemed necessary.
288 - 290	1	**Proposed change:** “The following information should be communicated by the blood establishment to affected manufacturers of plasma derived medicinal products without undue delay after receipt of the information, if subsequent4 to donation:”	Not accepted. There is no need to qualify the word “delay” by inserting "undue". No change necessary.
291	1	**Comments:** Post donation information in case “it is found out that the donor did not meet the relevant donor health criteria”, should be changed. **Proposed change:** “...it is found out that the donor did not meet the relevant donor health criteria relevant to plasma safety and/or quality”	Proposal is accepted.
292 - 293	1	**Proposed change:** “b) A subsequent donation from a donor previously found negative for viral markers is found positive for	Refer to comment on line 293 (below).

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		any of the required viral markers;..."	
293	1	**Comments:** Footnote no. 5: states that "Communication of such cases should already be made on repeat positive results and not await confirmatory testing..". **Proposed change:** For operations where the confirmative test results are received within 5 working days, it should be allowed to await the confirmatory test result to reduce labour time and paperwork involved	It is considered acceptable to wait for 5 working days for confirmatory results and the footnote is reworded as follows: "Communication of such cases should already be made on repeat positive results and not await confirmatory testing unless procedures in place assure that confirmative test results are received within 5 working days. The length of time …"
294 - 295	1	**Comments:** "…to agreed procedures" should be changed. **Proposed change:** "…to specified and validated procedures"	Not accepted. Tests and procedures are described in agreements between the blood establishment and the PMF holder. To make the wording clearer it is changed to "…agreed procedures between manufacturer/PMF holder (if applicable) and blood establishment."
291 - 302	1	**Comments:** PPTA would like to share some considerations pertaining to look-back procedures. First, the receipt of look-back units is an ongoing process: it is not unlikely that many times new look-back units will be found to impact the same batch of product. Accordingly, evaluations may become a time-consuming activity.	Partly accepted. Based on the comment the paragraph is reworded.

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		Second, it has to be kept in mind that the application of an inventory hold of 60 days allows the removal of the majority of the last nonreactive donations involved in a look back report (last donation preceding a reactive one that is singled out during the screening at the plasma supplier level), which are those more likely expected to be window period donations. All other donations involved in a look-back report are very unlikely to contribute any viral load. The non-reactivity of the manufacturing plasma pool confirms this. Moreover, if the NAT testing on the plasma pool is non-reactive, the presence of specific and efficient removal/inactivation steps in the production process assures that the final product is inherently safe. **Proposed change:** The following numbered points describe the possible causes for the initiation of a look-back procedure: 1. Subsequent to donation it is found that the donor did not meet the relevant donor health criteria; 2. A subsequent donation from a donor previously found negative for viral markers is found positive for any of the viral markers (by serological testing for HBsAg, anti-HCV and anti-HIV-1/-2, NAT testing as mini-pools for HBV, HCV and HIV-1); 3. It is discovered that testing for viral markers has not been carried out according to agreed procedures; 4. Subsequent to donation the donor develops an	

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		infectious disease (other than HBV, HCV, HIV) caused by an agent potentially transmissible by plasma-derived products (see section 4.1); 5. Subsequent to donation the donor develops Creutzfeldt-Jakob disease (CJD or vCJD – see below) 6. The recipient of blood or a blood component develops post-transfusion infection which implicates or can be traced back to the donor. Based on this: • For point 1, if the results of the NAT testing at the minipool level are non-reactive, no further action is required. • For point 2, if the results of the NAT testing at the manufacturing pool level are non-reactive, no further action is required. • For points 3 to 6 a re-assessment of the documentation for each batch is necessary	
302	2	**Comments:** The sentence should be clarified to avoid any ambiguity. **Proposed change:** For these cases a look-back procedure should be initiated which consists of tracing previous donations and testing of any retained samples, when relevant, for	The comment is acceptable. Sentence is reworded for clarity.

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		at least 6 months prior to the last negative donation.	
302 - 303	1	**Comments:** "..tracing previous donations back for at least 6 months prior to the last negative donation and testing of any retained sample." **Proposed change:** Such a recommended time period depends on the virus, the window period, donation frequency and the sensitivity of the assay. The AK-Blut Votum (Germany) recommends 3 to 4 months which is more appropriate. Such a period could be shorter or longer and should be adapted to the respective conditions and not be strictly fixed to 6 months.	There is no legal document setting timelines for the look back. Therefore, a flexible approach scientifically justified could be accepted.
302 - 304	1	**Comments:** Based on the non-reactivity of the NAT testing on mini pools and virus doubling times, the look back period can be reduced to 30 days prior to the last NAT negative donation. The absence of NAT positive donations is further confirmed by NAT testing of manufacturing plasma pools. **Proposed change:** The look back procedure to be followed in the event of any of the above should be documented in a standard operating procedure. In case that a donor is found positive for any of the viral markers or if the donor develops an infectious disease caused by an agent	See comment above.

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		potentially transmissible by plasma-derived medicinal products, previous donations should be traced back for at least 6 months prior to the last negative donation and any retained samples should be tested, if available. If NAT testing of donations is performed, previous donations should be traced back for 30 days prior to the last negative donation. Any departure from a 6 month look back period should be clearly stated and adequately justified.	
308	2	**Comments:** Evaluation can require additional testing such as NAT. During the period that retest results are pending evaluation is initiated but not complete. To allow this highly desirable retesting, the sentence should be modified. **Proposed change:** "urgent evaluation should be initiated "	The comment is taken on board and “urgent” is replaced by “immediate”.
313	1	**Comments:** The cumulative look back units that might be present in that particular batch have no relevance for the safety of the product. In case the pool is non reactive in NAT, the corresponding low amount of infectivity would be removed/inactivated by the process steps. **Proposed change:** Delete or re-phrase as above	The monograph plasma for fractionation requires testing of pools for HCV by NAT. Not all pools are tested for all viruses by NAT (HIV; HBV; HAV; B19V). The comment is therefore not accepted. However, the proposed change from “…, the cumulative look back units that might be present in that particular batch…”to “…, the available information on the cumulative look back units that might be present in that particular batch…” is accepted.

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		Add the underlined to sentence 313: "…, the available information on the cumulative look back units that might be present in that particular batch…"	
316	1	**Comments:** The availability of a look back system has nothing to do with the release of an intermediate or finished product. **Proposed change :** Delete	Unfortunately the wording of the guideline text was not completely understood. The guideline text states that "a system for the compilation of the look-back units for every plasma pool should be in place:". Because the analysis of look back units in a pool should be part of the safety strategy to yield a safe plasma pool, it is therefore an essential part of the release procedure of finished products or intermediates. No change is deemed necessary.
326 - 329	1	**Comments:** This part is unclear. Any processed vCJD donation results in a withdrawal of the batch. Information on a classical CJD donation has no relevance for vCJD and will not result in a withdrawal of the respective batch. **Proposed change:** Clarify for CJD and vCJD	Accepted. The text has been clarified.
330 - 334	2	**Comments:** These statements seem a bit redundant.	The comment is accepted and the paragraph deleted.
362 -365	3	**Comments:** A description of all relevant procedures for the preparation and the sampling of the plasma pools should be provided according to guideline EMEA/CHMP/BWP/3794/03, in part 3.2.S of the dossier	The information of plasma for fractionation can either be provided as a separate PMF or included in 3.2.S. To make this sentence more clear the wording is revised as follows: "A description of all relevant procedures for the preparation and the sampling of the plasma pools should be provided

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		of the medicinal product or a reference to the relevant PMF(s) can be given. This would implicate that the information concerning the list of specifications for the plasma pool is made available in both section 3.2.S and the PMF. The assessment of this information is part of the certification procedure of PMFs. The proposed procedure would lead to possibly a different outcome of the assessment of the PMF and 3.2.S. **Proposed change:** A description of all relevant procedures for the preparation and the sampling of the plasma pools should be provided according to guideline EMEA/CHMP/BWP/3794/03, in part 3.2.S of the dossier of the medicinal product a reference to the relevant PMF(s) should be provided.	according to guideline EMEA/CHMP/BWP/3794/03, in part 3.2.S of the dossier of the medicinal product or by means of a reference to the ~~relevant~~ PMF(s) ~~can be given~~ where relevant."
389	2	**Comments:** Line 389-391 comments on the use of alternative intermediates used in product manufacture. It is accepted that no two manufacturers will have identical process and intermediates may not be interchangeable. However, industry needs the flexibility to exchange intermediates and there are guidelines on compatibility studies that can and are followed to establish the suitability of using alternative intermediates (not necessarily early stage intermediates). These	Partly accepted. The European Commission's position is to not accept alternative processes for biological products since they are in part defined by reference to the method of manufacture. However, a variant of an established process for intermediate plasma fractions may be acceptable e.g. filtration or centrifugation in the fractionation process, the use of an optional step for the capture of e.g. Antithrombin III in the manufacturing of immunoglobulins. This has been clarified in the guideline. The guideline requires

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		compatibility studies to validate these intermediates are mentioned three paragraphs away from the initial statement and should be incorporated into the paragraph starting on line 389 for better clarity and readability. **Proposed change:** See above	that all variants of a process should be validated on their own.
389 - 394	1	**Comments:** There is a separate Guideline available for the change of production processes (CHMP/ICH/5721). Citation of this guideline is sufficient. **Proposed change:** Delete	See above. Furthermore, the guideline CHMP/ICH/5721 addresses the change of process and not the use of alternative processes in parallel. Although the principles laid down in the guideline are relevant for the justification of the alternative process as such, the use of alternative processes in parallel is not acceptable in general for biological products. Please see comment above.
392 - 394	1	“However, a variant of an established process may be employed if it concerns an intermediate used at an early stage of the manufacturing process of the medicinal product and if it does not concern the steps for viral reduction.” **Comment:** Further explanation is requested for clarity in regards to the meaning and how to determine or demonstrate when a variant does not involve viral reduction step(s). **Proposed change:** The sentence“..if it does not concern the steps for viral	No longer relevant in view of rewording.

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		reduction" should be re-phrased to "…if it does not concern validated steps for viral reduction claimed in the product registration file."	
395 - 398	1	"The suitability of use of the alternatives intermediates must be demonstrated by the manufacturer. In the assessment of possible impact on quality, the process for production of the alternative intermediates should be validated as such, and it should be validated that the use of the alternative intermediate does not affect the quality and viral safety of the finished product." **Comments:** It is recommended to maintain existing wording provided in CPMP/BWP/269/95, version 3.0, section 3.2.4 Intermediates, which provides more clarity than the proposed change. **Proposed change:** Change sentence to read: "The suitability of use of the alternative intermediates must be demonstrated by the finished goods manufacturer."	The text was changed in the light of the European Commission's position not to accept alternative processes for a biological product (see above). Since the wording in the existing text is not fully in compliance with this position, the existing text is reworded.
401 – 406	1	**Comments:** Superseded tests also result in non-reactive manufacturing pools and virus safe products. Risk assessments should be made only in case the superseded tests were demonstrated to be unsuitable due to wrong test results, which have impact on viral safety. In case new, e.g. more sensitive, test have been	The intention with this paragraph is to avoid that the current requirements of plasma testing is not fulfilled (e.g. new test requirement for a new adventitious agent or a new type of testing) because of cumulative storage periods of intermediates. For intermediates, the manufacturer of the finished product should always propose a shelf life which should be approved by

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		established, not necessarily a risk assessment has to be performed. **Proposed change:** Remove lines 404 to 406 Add the underlined: "Final product manufacturer shall ensure that storage periods for intermediates are set for use in the manufacture of the final product and justified by stability data." **Comment:** In regards to Annex 14, PPTA submitted to EMEA the following suggested change: "For intermediate products with an expiry date, a shelf-life should be defined by the manufacturer of the intermediate. The manufacturer of the finished product is responsible to decide, whether the shelf life is appropriate."	the competent authority. The second sentence on line 401 is reworded to be more clear: "When releasing a final product produced from a stored intermediate, the finished product manufacturer should ensure that at the time of release the product meets current requirements regarding the risk of transmission of infectious agents."
411	4	"...inactivation and/or removal of potential microbial contaminants." Reduction of microbial contamination is usually validated for sterile filtration steps - I assume it should read ….inactivation and/or removal of potential viral contaminants.	The sentence on line 409-411 is reworded as follows: "Manufacturing strategies vary according to product and manufacturer, and usually include several fractionation/purification procedures, some of which may also contribute to the inactivation and/or removal of potential adventitious agents.
413 - 416	1	**Comments:** Please see comments on lines 389 – 394; redundant **Proposed change:**	See comments above for lines 389-394.

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		Delete	
410 - 411	1	"… some of which may also contribute to the inactivation and/or removal of potential microbial contaminants." **Comments:** Microbial contamination is not the major concern; in addition, the reduction of microbial contamination is usually validated for sterile filtration steps. **Proposed change:** "… some of which may also contribute to the inactivation and/or removal of potential viral contaminants. " [potentially: … some of which may also contribute to the inactivation and/or removal of potential microbial and especially viral contaminants.]	See comment above.
442 - 443	4	(see also 8.2 below)…	The reference is changed to 8.2.
443	1	**Comments:** "…also 4.5.2 below" **Proposed change:** 4.5.2 does not exist in this document, replace by "… also 8.2 below)".	The reference is changed to 8.2.
451	2 and 4	**Comments:** Typographical-mistake	Typographical mistake is corrected.

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		Proposed change: Chromatographic	
464 - 465	2	**Comments:** To clarify that such control are not requested on a routine basis if adequate evaluation has been conducted, the sentence should be modified for clarification. **Proposed change:** The materials, their use and residual concentrations in the final product should be documented.	The comment is acceptable. The sentence on line 464 to 465 is changed to: "The materials, their use and residual concentrations in the finished product should be documented ~~and their use should be documented and their residual concentrations measured in the final product.~~ The residual concentrations should be measured in the final product unless acceptable and consistent results have been demonstrated."
463 - 466	1	**Comments:** Final product concentrations of substances added during the fractionation/manufacturing process used are dependent on the product specific methodologies used. The impact on final product safety and efficacy is evaluated during product development and in the product licensing process. **Proposed change:** Measuring of residual concentrations in the final product should only be required in accordance with the licensed final product specification.	See above.
474 - 475	1	**Comments:** In case upper and lower limit of the manufacturing process have been investigated in virus validation	Worst case condition means a situation using the least favourable conditions for viral reduction.

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		studies are additional studies on robustness not required? **Proposed change:** Please clarify	
484	1	**Comments:** "..accuracy of the modelling..." **Proposed change:** It should be clarified whether the "suitability" of modelling is meant.	It is agreed that "suitability of the modelling" is better wording here.
517	2	**Comments:** Line 517 states that "Reprocessing should only be performed in case of process failures." Can the MAA holder state its policy for reprocessing in the licence dossier or must these incidents be a batch specific variation? Past experience is that these can only be batch specific variations and if that is the case then it should be stated in this guideline.	For re-processing which is only acceptable in case of process failures and which is possible to foresee, the procedures and criteria should be described in the dossier. No batch to batch specific variation is considered necessary.
535 - 537	2	**Comments:** If a process has been duly validated, such a testing should not be required on a routine basis. **Proposed change:** Add to line 537 at the end of the paragraph: "adequate validation may avoid the requirement to conduct such	The comment is acceptable since it is in line with Q6B. The following additional sentence is added to line 537: "For certain parameters, testing of either the drug substance or the drug product may not be necessary on a routine basis and may not need to be included in the specifications if efficient control or acceptable and consistent results have been satisfactorily demonstrated."

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		assay on a routine basis".	
560 - 561	1	**Proposed change:** Add the underlined “The manufacturer of the finished product shall ensure that stability studies on the intermediate and, unless otherwise justified, on the finished product should also be performed if an intermediate from an external manufacturing site is introduced.”	The comment is accepted. To make it clear who is responsible the “MAH” is mentioned: “The MAH should ensure that stability studies on the intermediate and, unless otherwise justified, on the finished product are performed if an intermediate from an external manufacturing site is introduced.”
579	2	**Comments:** Is there evidence that circoviruses are transmissable by blood or plasma products?	Circoviruses were mentioned as an example for very small viruses in order to illustrate the technical difficulties to eliminate all known non-enveloped viruses. No clinical symptoms or pathogenicity have been associated so far with viruses such as TTV. TTV and SEN-V can be found in human plasma. No modification of text is considered necessary.
579	1	**Proposed change:** replace “…small viruses might penetrate even small filters …” with “…small viruses might penetrate even virus filters with small pore sizes …”	Text modified.
582	2	**Comments:** It is suggested that the introduction of safer products to the market within a reasonable timescale requires action by the manufacturer but also facilitation by control authorities.	Requirements for clinical data are a case by case decision and depend on the impact of the change on quality attributes and respective clinical guidelines. No modification is necessary.

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		Proposed change: after "Manufacturers are encouraged to develop/implement complementary process steps designed to remove or inactivate a wide spectrum of viruses, add "Authorities are encouraged to facilitate introduction of such additional steps in existing product by minimising the requirement for clinical data when the additional steps are known to be both efficient in virus removal or inactivation and known to have no impact on protein structure and integrity."	
582 - 584	4	"It is recognised ….is not a straightforward task." This sentence is difficult to understand (even it was already in rev. 3 and rev. 2!) in my opinion. I guess the meaning of the sentence is that designing steps may be difficult to achieve the goal of improved virus safety without lowered protein integrity/overall product quality. This should be stated, especially as in Line 593 - 594 "Manufacturers should apply their best effort to develop methods to inactivate/remove viruses and this should be a continuous process", EMEA is asking to develop (complementary) steps.	No modification is considered necessary.
590 - 592	2	**Comments:** Coagulation factors are a poor and inaccurate example here. Nanofiltration has been successfully introduced in a large number of Factor IX products and reduction factors against PV B19 are remarkable. One FVIII	Text modified according to the proposed change.

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		product is also 15 nm nanofiltered with excellent results against B19. This example is potentially misleading and should be deleted. **Proposed change:** Also, there may be viruses potentially present in plasma that are resistant to the inactivation/removal methods that can currently be applied to a particular class of product.	
592	1	**Comments:** Parvo B19 is not a good example, as Blümel et al. demonstrated effective inactivation of B19 by heat treatment. **Proposed change:** Explain cases of resistance of Parvovirus B19: e.g. Solvent/Detergent Treatment and add citation Blümel et al.	Text modified according to proposed change from IPFA given above.
599 - 600	4	"Partition processes such as fractionation or purification procedures (e.g. immunoaffinity chromatography) may contribute to virus removal." I agree that partitioning steps contribute and may even be effective reduction steps - but "immunoaffinity"-chromatography is a wrong example in my opinion (e.g. the column can usually not be sanitised thoroughly); therefore, I propose to state just "(e.g., chromatography)".	Chromatographic methods other than immunoaffinity may contribute towards virus reduction as well. It is agreed to state just “chromatography”.
608 - 611	1	**Comments:**	Partly accepted. The text clearly says that there is a possibility that a partitioning step could fulfil the criteria for an effective

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		Please see comments to lines 443 – 445: Regulatory authorities should be assured and convinced that manufacturers can control the steps and can separate the fractions, as regulators have licensed the products based on submitted data. There is no reason not to accept partitioning steps and their contribution to virus removal as those steps are well controlled, specified etc. and robustness has been demonstrated, as well as reproducibility of virus reduction. Please see: Dichtelmüller H et al.; A General Approach to Robustness Studies for Virus Inactivating and Partitioning Steps Used in Production of Plasma Derivatives; BioProcess International Suppl. Nov 2005 and Dichtelmüller H; Virus Removal by Steps of the Cold Ethanol Fractionation Process: A Review; Viral Safety for Biologicals; Cologne June 2009 **Proposed change:** Change "...then it could fit the criteria of an effective step." into "… then the respective step is an effective step"	step if various requirements are met. In addition, the following is added: "Previous experience can be taken into account to design experiments for validation of virus removal by fractionation
616 - 618	2	**Comments:** Is there any reference or evidence to support this example? If not we suggest it be deleted.	Comment accepted and example deleted. ~~For example, a solvent detergent/step might break up aggregates and allow more non-enveloped virus though a subsequent filtration step to remove viruses.~~
618 - 623	2	**Comments:** The list provides examples but cannot be exhaustive.	The example is considered helpful. The text: Consideration should be given to the maintenance of

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		We would recommend to simply refer to the appropriate NfG. **Proposed change:** Consideration should be given to the maintenance of the integrity of the components of the plasma derivative.	the integrity and functions of the components of the plasma derivative, e.g. to the potential formation of neoantigens, the possibility of enhanced thrombogenicity, and the possibility of toxic residues from chemicals used in the process is kept. However, the sentence “Separate guidance is available on clinical studies that should be undertaken” is deleted.
637	1	**Comments:** Viruses are precipitated prior addition of filter aids. Usually filter aids do not adsorb or bind viruses, but can enhance separation of fractions and therefore result in more efficient separation of virus containing and virus deprived fractions. **Proposed change:** Change into: .." they can enhance the viral removal capacity of the separation process.”	Modified as proposed.
641	1	**Comments:** Pasteurization is only one example of wet heat treatment. Inactivation by wet heat treatment results in effective virus inactivation too at lower temperatures at longer incubation time. Even at 37°C or even 21°C reliable and effective virus inactivation can be achieved at long incubation times. **Proposed change:** Add the underlined: “The efficacy of such a treatment is dependent upon the composition of the solution, the	Text is changed as proposed.

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		temperature and incubation time.”	
641		Typo - pasteurisation	
648	1	**Comments:** The upper limit of residual moisture represents a best case condition. Virus validation thus should be done at worst case conditions (lower limit of residual moisture). The upper limit is of interest only for the process validation, not for viral safety. **Proposed change:** Lower limits of residual moisture should be set based on virus validation studies and upper limits based on protein integrity studies and aggregate formation studies.	Range of residual moisture should be validated. No change to the text is necessary.
652	2	**Comments:** Unlike temperature or duration, residual moisture, even with NIR, cannot be monitored continuously throughout the process. In addition NIR is not yet validated for all products. However we agree NIT testing should be validated and performed at critical points in the process. **Proposed change:** We propose "Critical parameters must be monitored carefully; in particular temperature and duration of heating should be monitored throughout the process. Where possible residual moisture should be carefully	Modified wording included: Residual moisture is a particularly critical parameter and should be preferably measured on each vial with non-destructive methods (e.g. by near infrared spectroscopy). Temperature and duration of heating should be monitored throughout the process step.

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		monitored, preferably measured on each vial with non destructive methods (e.g. by near infrared spectroscopy)"	
654	1	**Comments:** Solvent/Detergent (S/D) treatment is an established procedure for virus inactivation in medicinal products derived from human plasma for more than 20 years. Data on the inactivation of enveloped viruses by S/D treatment collected from seven PPTA member companies demonstrate the robustness, reliability and efficacy of this virus inactivation method. The data from 308 studies using production conditions and beyond were evaluated, comprising different methods of S/D treatment (TNBP/Na-Cholate, TNBP/Tween 80, TNBP/Triton X-100) and different plasma derived medicinal products (Factor VIII, Factor IX as well as intravenous. and intramuscular. immunoglobulins). Neither product class, pH, protein concentration nor temperature appeared to have significant impact on virus inactivation. A parameter that did appear to be critical was the concentration of solvent and detergent. The data demonstrate the robustness of virus inactivation by S/D treatment for a broad spectrum of enveloped test viruses and of process parameters. The PPTA data collection has recently been accepted for publication by Transfusion (Dichtelmüller et al.Transfusion 2009.49:1931-1943). **Proposed change:**	The comment is not fully correct. Temperature might have a significant impact on virus inactivation (e.g. when using Tween 80 at temperatures of 4°C). This is not clear from the publication. However, it is agreed that much knowledge about parameters influencing SD treatment has been accumulated in the last years. An additional paragraph is included: Solvent/Detergent (S/D) treatment is an established procedure for virus inactivation. Previous experience can be taken into account to design experiments for validation of virus inactivation. This can be helpful to limit the number of product-specific validation runs to the determination of virus inactivation kinetics at “worst case” conditions (e.g. lower manufacturing limits for concentration of SD-reagents and temperature).

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		We would propose introducing a reference to Dichtelmüller et al and take the findings into account, when defining the level of validation. In view of the abundance of supportive data and experience, we do not see the need for extensive validation studies.	
665 - 666	2	**Comments:** Is there any reference or evidence to support this? If not please delete.	The recommendation is based on the original development done by Horowitz et al.
669	1	**Proposed change:** Change title “Filtration” to “Virus Reduction Filtration”. This matches title in line 784 and is more consistent with previous wording from version 3.	Title is changed as proposed.
675	1	**Proposed change:** (e.g., volume per filter area, conductivity, pH, flow rate, pressure and protein load)	Text is changed as proposed.
675	4	**Proposed change:** "(e.g., volume per filter area, ionic strength (or conductivity), pH, flow rate, pressure and protein loading)"	See above.
705	2	**Comments:** Factor von Willebrand is missing. Please add it. **Proposed change:** For Factor VIII (and factor VIII/von Willebrand), factor	Comment is accepted.

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		von Willebrand and fibrinogen products, …	
709	1	**Comments:** Parvovirus B19 can be effectively inactivated even in coagulation factors by heat treatment or can be removed by virus filtration, e.g. in F IX solution, depending on the pore size. **Proposed change:** Please add citation: Blümel et al, Transfusion 2008, vol 48; pp790-791: Human parvovirus B19 can be inactivated by heat, but animal parvoviruses are more heat resistant than B19V.	Not all heat-treatments applied to coagulation factors have been shown to be effective for B19V inactivation. The text is modified to take account of the comment: It is recognised that some viruses (e.g. animal parvoviruses) are very resistant to physico-chemical methods for virus inactivation and that development of an effective inactivation/removal step may be difficult for this type of virus. Parvovirus B19 may be inactivated by carefully-designed heat treatment steps (pasteurisation in an appropriate matrix or dry heat treatment at appropriate residual moisture). Parvoviruses may be removed by virus filtration depending on the pore sizes applicable to the coagulation factors.
708 - 710	2	**Comments:** The reader is left without guidance here.	See above for guidance.
717	1	**Comments:** Ethanol fractionation steps are adequately controlled and validated and show reproducible virus reduction. **Proposed change:** ".... fractionation/precipitation steps <u>should</u> be accepted as effective for virus removal, as they are adequately controlled and validated."	Fractionation steps might not be adequately controlled in each case. Therefore, the wording “can be adequately controlled” is considered appropriate. It is not deemed necessary to change the wording.
721	4	I just do not know, but I doubt that a 15 nm filter is employed in the production process of immunoglobulins	It is possible to apply a 15N Filter.

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		- 20 nm definitely.	
727	2	**Comments:** What is the rationale for considering the effect of albumin concentration on virus reduction? And what exactly is meant by "considered"?	See below.
727 - 728	1	**Comments:** Pasteurization of Human Albumin is a well defined process and described in the Pharmacopeias (e.g. US, EU etc). There is little possibility to change this process step against the Pharmacopeia. Extensive virus validation studies on pasteurization thus can be omitted. The other steps of the manufacturing process of albumin are steps of the cold ethanol fractionation process. In case cold ethanol fractionation is accepted as a virus removal step for Albumin, it should also be valid for immunoglobulins. - The effect of albumin concentration on virus inactivation can be neglected, at least for pasteurization: 5% and 20% and 25% Albumin shows no difference in inactivation kinetics Proposed change: Please clarify extend of robustness studies for Pasteurization or give a statement that robustness for this step must be demonstrated only for deviating conditions than described in Pharmacopeias.	Sometimes, slightly different inactivation kinetics have been observed for 5% and 20% or 25% albumin. The sentence has been revised to “Validation of the pasteurisation step should consider the nominal concentration of the finished product.”
729	4	S/D Plasma: Line 733 - 734 "There remains a theoretical risk from newly emerging non-enveloped	The comment is accepted. The wording is revised by deleting “adequate” in line 730 and replacing “theoretical risk” by

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		viruses". Comparing this phrase with Line 594 - 595 "Previous experience clearly shows that starting material may contain unknown viruses and that new viruses may appear", the risk of S/D plasma to transmit unknown viruses seems to assumed to be lower than of "classical" plasma-derived products which contain, however, further manufacturing steps at least contributing to the reduction of unknown viruses. A more balanced wording seems appropriate.	“potential risk”.
749 - 755	4	I propose to modify the order of model viruses to be used in virus validation studies to (most probably) more "resistant" virus and viruses used in most studies: "Various models have been used to validate virus inactivation methods including pestiviruses, e.g. bovine viral diarrhea virus, flaviviruses, e.g., yellow fever virus (is that really true - WNV or TBEV may be the more a often used flavivirus), and togaviruses e.g. Sindbis virus".	Comment is accepted and wording is changed as follows: Various models have been used to validate virus inactivation methods including pestiviruses, e.g. bovine viral diarrhoea virus, flaviviruses, e.g., WNV, TBEV or yellow fever virus, and togaviruses e.g. Sindbis virus".
751	4	Typo bovine viral diarrhea virus (without o).	UK English spelling is with o.
753 - 755	1	**Comment:** The example is incorrect as Scheiblauer et al. (1996) demonstrated that a togavirus (SFV) was reduced by 4.6 log10 and a pestivirus (BVDV) was reduced by 1.6 log10. However, Yei et al. (1992) demonstrated for HCV a reduction factor in the order of more than 4 log10, therefore, HCV resembles togaviruses and not pestiviruses more closely.	The comment is accepted and the wording revised to: “For example, there is evidence that pestiviruses differ in their partition in the Cohn Oncley fractionation process from togaviruses ~~and that HCV resembles the pestiviruses more closely in this respect.~~ Currently, there are insufficient data on HCV to identify the most appropriate model virus for validation studies. Therefore, caution is required in the choice of model virus and in the interpretation of validation data. The pestivirus BVDV may be more difficult to reduce in some partioninig steps

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		Proposed change: Use other or erase example.	and it may be more resistant at low pH than other model flaviviruses. Therefore, BVDV could be considered as a “worst case model” for HCV
753 - 755	4	Example is not covered by publications - therefore, it should be erased (PPTA will comment on that topic): Scheiblauer et al. (1996) demonstrated that a togavirus (SFV) was reduced by 4.6 log10 and a pestivirus (BVDV) was reduced by 1.6 log10. However, Yei et al. (1992) demonstrated for HCV a reduction factor in the order of more than 4 log10; therefore, HCV resembles togaviruses and not pestiviruses more closely. It may be stated that BVDV is a more "resistant" virus - at least in some partitioning steps and should be, therefore, employed in virus validation studies.	See above.
761 – 762 763 - 769	1	**Comments:** Pseudorabies (PRV) is a widely used model virus for HBV (not for filtration: particle size!). Therefore PRV should be used in virus validation studies. PRV is more useful than Duck HBV. **Proposed change:** The section on DHBV can be removed, as it is extremely special and not for standard plasma derivatives.	The fact, that PRV is widely used as a model for HBV does not prove that the model reflects HBV. The wording is changed as follows:”…..(e.g. UV illumination) are highly virus strain dependent among enveloped viruses.”
779 - 781	4	"Studies using HAV and B19V are not required for immunoglobulins if the presence of protective levels of antibodies in the product can be assured." What is a protective level? For HAV there may be experience from HAV hyperimmunoglobulins, but to my knowledge there	It is agreed that protective levels of antibodies with respect to B19V have not yet been defined. The wording in line 778 to 783 is modified as follows: “Validation studies for coagulation factors should also include

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		are no data for B19V. The protective level has to be assured in batch release assays. As studies with non-enveloped viruses for which antibodies are unlikely to be present are requested, the data from these studies (or from studies in IgG intermediates without antibodies against HAV and B19V) should be used to assess the risk to transmit viruses.	an appropriate model for the B19V. Models that have been used include canine, porcine, murine and bovine parvoviruses. Studies using HAV and B19V are not required for immunoglobulins. However, data from non-antibody complexed model viruses may not adequately reflect reduction of HAV or B19V in intermediates where binding antibodies are present. Therefore it may be helpful (but not mandatory) to perform such studies in order to clarify the reduction capacity for HAV and/or B19V. In each case, studies with non-enveloped viruses for which antibodies are unlikely to be present should be performed to evaluate the ability of the process to inactivate/remove possible unknown non-enveloped viruses."
784	1	**Comments:** HIV BVDV are still required for validation studies for small pore size virus filters. For medium pore size filter herpesvirus are declared mandatory. **Proposed change:** This paragraph should be re-formulated in a way that if e.g. parvovirus is retained significantly, larger viruses don't have to be tested and the LRF obtained for parvovirus is applied for all other viruses (e.g. BVDV; HIV etc). The latter for example was applied in the flebogamma EPAR (http://www.emea.europa.eu/humandocs/PDFs/EPAR/flebogammadif/H-781-en6.pd)	The given example is a product-specific evaluation. In this evaluation the specific product intermediate, the specific type of filter, and context of other efficient virus reduction steps were considered. Such product-specific evaluation must not be extrapolated to a general situation, especially when the type of filter is not known. BVDV is one of the smallest viruses with some flexibility in shape and should be used especially for new filters. There has been a reduction of model viruses as requested in the former version of this guideline. This reduction is considered sufficient. No further changes are introduced.

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787	2	**Comments:** Specific circumstances should be mentioned where it may be difficult to measure removal solely by nanofiltration. **Proposed change:** … whatever the nanofiltration system used. In some circumstances (Immunoglobulin; pH; residual solvent/detergent…), virus inactivation can occur during nanofiltration with difficulty to quantify virus reduction solely by the nanofiltration step.	The comment is accepted and the following sentence added: "In some circumstances (Immunoglobulin; pH; residual solvent/detergent…), the quantification of virus removal solely by the filter may be rendered difficult because of virus inactivation/neutralisation that can occur during the nanofiltration."
825 - 827	1	**Comments:** "... required when relevant changes in the manufacturing..." Relevant changes are a very imprecise description. **Proposed change:** Please give examples for "relevant": e.g. change of fractionation site? Change of an IPC? Change of scale? Suggested re-phrasing: "required when major changes in the manufacturing process having influence on quality or safety of the final product…" Alternatively: give a link to the Guideline on Clinical Investigations /APMP/BPWG/388/95 rev1.	New virus validation studies are required when changes in the manufacturing process impact the virus inactivation/removal step(s). The wording is amended as follows: "New validation studies are required when relevant changes in the manufacturing process or in individual steps are being undertaken. The absence of new validation studies should be fully justified".
953 and 1013	2	**Comments:** It would be better to define the "established fractionation processes" for albumin. Does it comprise	The sentence was rephrased as follows: "A risk assessment will not be expected for new marketing applications or existing marketing authorisations in the case of

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		more processes than the various Cohn variants?	albumins manufactured according to European Pharmacopoeia specifications and with established Cohn or Kistler/Nitschmann fractionation processes.“
Paragraph 10 as whole	3	**Comments:** When a plasma product is used during the manufacturing of another medicinal product, full documentation is required about that particular plasma product. It is not clear what the added value of this request is; i.e. it is not clear in what way the quality of the product will benefit. However, the request for full documentation will considerably add to the workload of companies and authorities. Besides it is not clear what is meant by full documentation, does this include Module 3 only or is it a request for a full CTD?	See below.
981	1	**Comments:** For plasma derived products used in the manufacture and formulation of medicinal products, full documentation is requested for the plasma derived medicinal product used. The wording could be interpreted as a request for a complete Module 3 for the plasma derived product. However, the “guideline on excipients in the dossier for marketing authorizations - (EMEA/CHMP/QWP/396951/2006)” clearly defines the required documentation for excipients in medicinal products for human use. Plasma derived excipients are not excluded from the scope of this guideline. To avoid any misunderstanding or misinterpretation, a reference	Full documentation on plasma-derived products used in manufacture and/or formulation of medicinal products or as ancillary substances in medical devices is required. However, the comment was considered when plasma-derived products are used for which the starting material plasma is covered by a plasma master file. Documentation needed in this case is specified in the new wording of the guideline.

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		to this guideline should be included. Furthermore, for plasma derived medicinal products already registered in the community as therapeutic medicinal product, a reference to the registration should be sufficient. This avoids a cascade of variation procedures for medicinal products, whenever the registration documentation for the plasma derived product is varied. **Proposed change:** Documentation should be provided for the plasma derived medicinal product used as outlined in GUIDELINE ON EXCIPIENTS IN THE DOSSIER FOR APPLICATION FOR MARKETING AUTHORISATION OF A MEDICINAL PRODUCT (EMEA/CHMP/QWP/396951/2006). For plasma derived medicinal products registered in the community as therapeutic medicinal product, a reference to the registration is sufficient. The plasma-derived medicinal product used in the manufacture should always be within its shelf-life and, therefore, within its pharmacopoeial/marketing authorization specification at the time when it is incorporated into a starting material, intermediate, final product or medical device. A corresponding confirmation should be provided.	
1013 - 1017	2	**Comments:** These phrases seem in contradiction to each other where albumin is concerned.	The paragraph is not modified as it is not a contradiction but a warning statement. This paragraph is also present in the current version of the guideline – only one sentence has been deleted i.e. 'The development of substitutes for plasma-derived

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			albumin as an excipient for medicinal products is encouraged.
Annex I	2	**Comments:** In Annex I there are two references to Annex I. This is clearly a typographical error.	The typographical error is corrected.