EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 June 2013
EMA/CHMP/BWP/661511/2012
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Reflection paper on the use of starting materials and intermediates collected from different sources in the manufacturing of non-recombinant biological medicinal products' (EMA/CHMP/BWP/729106/2011)*

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

Stakeholder no.	Name of organisation or individual
1	ALK-Abelló A/S
2	APIC
3	CSL Behring / CSL Ltd.
4	EBE (European Biopharmaceutical Enterprises)
5	EGA (European Generic medicines Association)
6	GSK
7	Kamada Ltd.
8	LEO Pharma
9	Sandoz GmbH
10	IPFA

* This document was initially released for external consultation as 'Reflection paper on the use of starting materials and intermediates collected from different sources in the manufacturing of non-recombinant biological medicinal products'. Due to the nature of the content and the recommendations provided it has been renamed as 'Guideline'.

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1. General comments – overview

Stakeholder no.	General comment	Outcome (if applicable)
1	ALK does not find that the reflection paper, in the current form, is adding any additional guidance relevant for allergens and accordingly ALK suggests removing allergens from the scope of the reflection paper. Although it is stated in the reflection paper that it clarifies the definition of starting materials, the reflection paper does not define starting materials for allergens. Starting materials for allergens are adequately defined in the EMA guideline on allergen products: Production and quality issues (CHMP/BWP/304831/2007). Considering the concept of accepting process variability it is quite difficult to relate allergens to the major examples given in the reflection paper and again, the concept of process variability is already addressed in the EMA allergen guideline: "…If source materials from different suppliers and deliveries are mixed to achieve uniform source material batches, the underlying concept should be described. Uniformity of the source material from different origins should be justified" (CHMP/BWP/304831/2007).	Comments appreciated. Allergens were not mentioned in the document as one of the major examples, but they would in principle be within the scope of the document, i.e. biological medicinal products which contain active substance extracted from organs, tissues or fluids from living organisms, either of animal or plant origin and for which flexibility of sourcing in the biological starting materials may be needed to ensure product supply. This was also based on the fact that allergens are mentioned in the GMP Annex 2 in the same category as e.g. heparins. However, it is acknowledged that the main issues (definition of starting material, flexibility in sourcing, comparability) as outlined in the current document are sufficiently detailed in current available guidance for allergens. Therefore, allergen products will not be further discussed in the guideline.
2	The reflection paper is not clear on the definition of "different sources". The text seems to differentiate between sourcing IN versus sourcing OUTSIDE of the EU. Also the phrasing "third countries" seems to refer to countries outside of the EU. This should however be clarified. The definition may have consequences for MAHs and drug substance	Comments partly accepted. Document will be amended to better clarify "different sources". The guideline did not intend to differentiate between IN vs. OUTSIDE of the EU.

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	manufacturers and their change control procedures (e.g. introducing a new source within the EU vs. introducing a new source outside of the EU – difference in regulatory consequences?).	
4	In Section 2 of the paper is it seems to be suggested that flexibility in sourcing to ensure product supply is defined as sourcing in versus outside the European Union. This suggestion is repeated in the last paragraph in Section 4: "GMP measures should be adequate to ensure an appropriate control while allowing sourcing of starting materials for early intermediates biological products in different locations from third countries." "Third countries" is interpreted as countries outside the European Union. The paper should provide more clarity on EMA's view on the consequences for marketing authorization holders and drug substance manufacturers when sourcing in the EU versus outside the EU.	See previous point.
4	It should be clarified in the Scope that the reflection paper addresses starting material quality requirement to support a Marketing Authorisation Application and does not delineate new requirements for biological medicinal products already on the market.	Not accepted. Marketing Authorisation dossier for already licensed products should be updated at the earliest regulatory time point.
5	The reflection paper clearly focuses on products manufactured from naturally occurring, non-recombinant products. However, this is not stated in the title or text body. This is why some statements are confusing, especially the phrase "one process = one product", as comparability is a well-established concept for recombinant biologics. We therefore ask EMA to make clear, both in the title and in the text body, that this reflection paper deals with non-recombinant products only.	Comments appreciated. Document will be amended to clarify that the guideline deals with products from non-recombinant origin. Nevertheless, it should be noted that even in case comparability is demonstrated between two processes, only one licensed process is acceptable within a given MA for both non-recombinant and recombinant products.
6	We are supportive of the positive steps forward within this reflection paper, in particular we note that EMA is agreed with the principle of	Compliance with the Ph. Eur is mandatory but does not waive the need for detailed information on materials from

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	"one process = one product". However, in the specific case of heparins, we propose that the emphasis given to the importance of change occurring to manufacturing steps before the isolation of heparin is amended. We propose that control of heparin is appropriately assured through compliance with the Ph. Eur. Monograph.	different sources are used to support comparability. Comparability is beyond compliance with specifications.
7	Kamada Ltd would like confirmation that information relating to the manufacture of early intermediates can be included in 'Module 3.2.S.2.3, Control of Materials' rather than in '3.2.S.2.2, Description of Manufacturing Process and Process Controls' in order to clearly differentiate between the manufacturing steps performed by the early intermediate manufacturer and those performed by the drug substance manufacturer.	Strictly speaking all information about material manipulation starting with the porcine mucosa and its control should be included in the section '3.2.S.2.2, Description of Manufacturing Process and Process Controls'. Information pertaining to the selection and preparation of the mucosa could be included in 'Module 3.2.S.2.3, Control of Materials'.
10	As discussed at the Meeting of European Medicines Agency staff with IPFA and PPTA on 09 March 2012, IPFA point of view is that - in particular, this causes complexity for products undergoing multi-source processes - as stated in the Concept paper, o examples of such products are heparins (including LMWH), urine derived products like gonadotropins and urokinases, and plasma derived medicinal products o for these products, variability in sourcing and/or initial manufacturing steps has traditionally been allowed in contrast to the well characterised biotechnological products of recombinant origin for which the declared manufacturing process starts from a unique and well identified cell bank system	Partly accepted. Plasma derived product would, in principle be within the scope of the document, i.e. biological medicinal products which contain active substance extracted from organs, tissues or fluids from living organisms, either of animal or plant origin and for which flexibility of sourcing in the biological starting materials may be needed to ensure product supply. However, it is acknowledged that the main issues (definition of starting material, flexibility in sourcing, comparability) as outlined in the current document are sufficiently detailed in current available guidance for plasma derived products. As such, this product class will not be included in de document to provide further guidance on.

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	o this paper addresses to which extent any variability in the early manufacturing steps for certain biological products would be acceptable - this paper was conceived to harmonize dossiers requirements, especially for heparin derived products - alternative paths for blood products manufacturing are described and covered by ICH whereby quality attributes related to finished products (that are not singuidelinee from a starting material –e.g. FVIII vs VWF, which brings more complexity) are already taken into account - moreover, since blood products are covered by PMF, this guideline should not have any impact on the plasma-derived source material - also Annex 14 already covers the issue of various source materials. Therefore, IPFA proposes to take plasma products out of the scope of this document.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 4-6	5	Please change title from “Reflection paper on the use of starting materials and intermediates collected from different sources in the manufacturing of biological medicinal products” to “Reflection paper on the use of starting materials and intermediates collected from different non-recombinant sources in the manufacturing of biological medicinal products” The reflection paper clearly focuses on products manufactured from naturally occurring, non-recombinant products. However, this is not stated in the title or text body. This is why some statements are confusing, especially the phrase “one process = one product”, as comparability is a well-established concept for recombinant biologics. Proposed change: We therefore ask EMA to make clear, both in the title and in the text body, that this reflection paper deals with non-recombinant products only.	Accepted.
Lines 29-31	5	Comment: The introduction contains the sentence “For biological medicinal products the interpretation of European legislation thus adheres to the principle of “one process = one product” as a general paradigm, i.e. the	Not accepted. However, it is recognised that the statement “one process = one product” might be somewhat misleading and not scientifically valid for all discussion and will be further clarified in the guideline.

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		product is process specific." The concept "one process = one product" is scientifically obsolete. For that reason and because this phrase has been and is still used broadly by certain interested parties to discriminate against biosimilars, preventing broader patient access and better affordability, this phrase should not be used any more. Fact is that biologics undergo manufacturing and raw material changes in a very well controlled way today. This reflection paper will further add to this level of control. The comparability concept and the evaluation of manufacturing and raw material changes by EMA based on comparability data has in fact worked so well that the safety and efficacy of products could be warranted even after major changes. This is due to advances in raw material control, process science and analytical science. Analytical science allows us to fully understand biologics today, rendering therefore the old paradigm "the product is process specific" obsolete. The fact that the same product quality, safety, and efficacy can be achieved by different processes is also stronguideliney endorsed by EMA's experience with biosimilars.	

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		All 14 biosimilars approved by the European Commission after thorough scientific assessment by the CHMP/EMA since 2006 have been demonstrating in-market safety profiles indistinguishable from those of their reference products. Proposed change: Remove the sentence entirely<br ~~"For biological medicinal products the interpretation of European legislation thus adheres to the principle of "one process = one product" as a general paradigm, i.e. the product is process specific."~~	
Lines 37 – 39 (Introductio n)	1	Comment: Please refer to the General comment. Proposed change: Please consider to remove allergens from the Introduction to this reflection paper. "This applies also to products from non-recombinant origin that are considered as biological active substances/biological medicinal products in the current legislation ~~(e.g. allergens)~~."	Accepted.
Lines 40-41	4	Comment: the word "certain" has to be clarified	Accepted.
Lines 43-45 and 49-51	8	Comment: With respect to the adequate description of the manufacturing process in the marketing authorisation dossier, is there a scaled expectation for the level of information to be filed for earlier stages? Proposed change: LEO Pharma proposes that the detail	Partly accepted. The level of detail of process elements should be in line with the relevancy based on a risk assessment and as such a clear cut gradient scale of detail as suggest by the stakeholder cannot be given.

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		required for the marketing authorisation should also be a gradient scale of detail from early stages to the later purification stage. Given the considerable variation that may occur in the early stages of processing in relation to vessel size and handling capabilities of individual early stage processors, it is vital that the level of detail required is not excessively detailed as to prevent such inevitable processing variability to exist.	
Line 50	8	Comment: Given the nature of the animal tissue which is associated with the mucosa material (LMWH starting material) a number of physical tissue manipulations are required before the mucosa is available. These steps are not considered part of the biological manufacturing process. These steps are associated with the food industry in the isolation of casings. The by-product of this food industry process is the starting material of the LMWH process.	Accepted. The guideline indicates porcine mucosa as the starting material. As such, any manipulation before the mucosa is not considered as being part of the manufacturing process. This kind of information could be included in section '3.2.S.2.3, Control of Materials'.
Line 51	2	Comment: A clearer description of multi-source processes is needed. If sourcing is done in several places within one country and manufacturing steps applied are the same, is that multi sourcing?	Accepted. "Multi-sourcing" will be further described.
Line 51	4	Comment: A definition of multi-source processes is needed. Multi-source processes can be interpreted in different ways. It is not clear in this definition whether similar processing of mucosa sourced from different slaughterhouses in the same country, but under the same level of control, is considered to be a singuidelinee source or a multi-source process.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Suggest including a definition of multi-source processes.	
Lines 69-72	5	Please change scope from “This position statement addresses to what extent any variability may be acceptable in the early manufacturing steps for biological medicinal products which contain active substance extracted from organs, tissues or fluids from living organisms, either of animal or plant origin and for which flexibility of sourcing in the biological starting materials may be needed to ensure product supply.” to “This position statement addresses to what extent any variability may be acceptable in the early manufacturing steps for biological medicinal products of non-recombinant origin which contain active substance extracted from organs, tissues or fluids from living organisms, either of animal or plant origin and for which flexibility of sourcing in the biological starting materials may be needed to ensure product supply.”	Partly accepted. From the scope it is evident that the document deals with materials extracted from organs, tissues or fluids from living organisms either of animal or plant origin and. as such recombinant materials are excluded. However, it is noted that the title of the document is amended.
Lines 72 – 77	1	Comment: Please refer to the General comment. 1. The reflection paper does not clarify the definition of starting materials for allergens 2. The use of variant processes for the three presented major examples of biologicals are not related to the manufacture of allergens	Accepted. See above comments on allergens.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Both elements are already adequately described in the EMA allergen guideline (CHMP/BWP/304831/2007). Please consider to remove allergens from the Scope of this reflection paper in order to avoid a possible conflict between the two documents. "…A number of major examples are given which illustrate the concept of accepting process variability. The principles outlined in this document could be applied to other biological medicinal products, for which flexibility of sourcing in the biological starting materials may be needed, e.g. porcine pancreas for insulin and pancreatin~~, and allergens~~. Allergens and Advanced Therapy Medicinal Products (ATMP) are excluded from the scope of this document".	
Line 72	2	Comment: This sentence seems to suggest that flexibility in sourcing is only acceptable to ensure product supply. Other reasons, such as pricing may also warrant the inclusion of other sources.	Not accepted. The scientific document does not intend to take into account economic aspects. It is recognised that the issue of product supply also involves economic aspects.
Line 74	6	Comment: A number of major examples are given which illustrate the concept of accepting process variability. Proposed change: The term concept could be replaced by context	Not accepted. Wording 'concept' more clearly describes the intention of the major examples.
Lines 79-80	4	Comment: In the current draft reference is made to applications for marketing authorisation pursuant to Articles 8 and 10(1) of amended Directive 2001/83/EC.	Accepted. This is a general remark that all relevant information on quality should be put in the MA dossier, not to indicate the scope of the document. The guideline is amended

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		Our understanding is that while Article 10(1) covers several types of application, e.g. biosimilar applications under Article 10.4, it does not cover other relevant types of applications such as “well-established used” applications under Article 10.a. This type of application should also be referred to in the final document.	to only refer to directive.
Lines 90-92 109-113 155-156	6	Comment: The definition for “process intermediates” is applicable to all steps leading to the final biological product, from the starting biological material=mucus to the purified heparin (pharmacopeal grade) Proposed change: it would be helpful to have the list of all steps considered as process intermediates provided within the text. It would be helpful to further define what an early intermediate is.	Partly accepted. It is not possible to have a list of all steps considered as process intermediate as this would be too specific for the current document. Term “early intermediate” has been reconsidered as it did not sufficiently reflect the current manufacturing practice in the case of heparins. A definition for “key” intermediate has been introduced.
Lines 97-99	4	Comment: EDQM has decided to exclude from the scope of the Certification procedure (CEP) biological active substances of non-recombinant origin that have been classified as "other biological substances" by the CMDh. Proposed change: to introduce this information	Accepted. There is no need to amend the document.
Lines 101-102	3	Comment: This sentence may be misunderstood with regard to plasma as starting material. For plasma, the concept of the stand-alone PMF applies, which includes the PMF certificate as a placeholder for the actual PMF data in a marketing authorisation dossier.	Plasma derived products will not be detailed in the document. See above comments on scope.

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		Proposed change: Amend “Consequently, this data should be part of the marketing authorisation dossier for new and existing marketing authorisations.” by the sentence: “In case of the starting material plasma, the data package can be replaced in the marketing authorisation dossier by respective EU PMF certificates covering the data for the plasma used.	
Line 109	4	Comment: Mucosa is defined as starting material. Is collection the beginning of this, or is it the first processing operations such as digestion of the mucosa?	Not accepted. The collected mucosa (or pool as suggested below) is considered the starting material in line with EC Directive 2001/83.
Line 109	4	Comment: Only addresses mucosa. What about hashed gut and strip gut? Proposed change: Replace “mucosa” with “porcine intestinal tissue.”	Partly accepted. The document will be amended based on the Ph.Eur. monograph for heparin sodium.: “porcine intestinal mucosa“.
Lines 109, 115	4	Comment : it should be added porcine hashed guts as starting material so as porcine mucosa	Not accepted. See previous comments. Ph.Eur. monograph for heparin sodium will be adhered.
Lines 109, 110 and 114 - 117	9	Comment: The Draft of EMA-Reflection paper clearly defines porcine mucosa as the starting material for heparin production and requires that Module 3 of the marketing authorization dossier should cover the whole manufacturing process starting from the sourcing of the mucosa. This would mean that manufacturers/MAHs would have to file numerous slaughterhouses in the dossier. This is hardly manageable, especially from the perspective of	Not accepted. It is acknowledged that the actual synthesis starts from the step in which heparin molecules are liberated from the tissue. However, in line with GMP Annex 2 revised, also information on the early steps, starting from the mucosa, is needed to assure the quality of the active substance. "starting material" and "1st step of a synthesis" do not have the same meaning. To start a first step, it is necessary to define a starting material. Thus, the two terms are not exclusive but complementary.

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		updating the dossier in timely manner without jeopardizing the market supply. This should be considered in alignment with the statement quoted in the line number 60 and 61 of the EMA-Reflection paper: "As manufacturers inevitably need to have several suppliers, flexibility in the sourcing of biological substances of non-recombinant origin may be needed to ensure product supply". Proposed change: Therefore we propose to define the starting point of heparin production with the “step in which heparin molecules are liberated from the tissue”. This is in alignment with the position of the 5th Heparin Characterization Workshop, held on August 14 and 15, 2012 in Rockville, USA. At this conference a presentation has been given by an FDA representative, Arthur B. Shaw, stating: "Step in which heparin molecules are liberated from the tissue is considered to the first step in the manufacturing process. All sites involved in processing from this step to the final product are expected to be identified and operate in compliance with CGMP." A harmonization between FDA and EMA with regard to the definition of the first step in the manufacturing process would be highly appreciated.	
Lines 109/120/129	2	Comment: porcine mucosa and human urine are defined as starting materials. For plasma the addition (pool) is made; please note that urine and mucosa are	Accepted.

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		also collected in pools. Proposed change: line 109 add (pool) after porcine mucosa line 120 add (pool) after human urine	
Lines, 111, 156 & 190	8	Comment: Reference is made to 'early intermediate' requirements in lines 156 and 190 and to 'partly purified crude heparin' in line 111. Clarification of these terms would be advantageous for all participants involved in the manufacture of biological medicinal products; perhaps such a discussion could be had with industry in the form of a BWP workshop to discuss the paper and ensure industry clearly understands the current thinking of the EMA in relation to biological sourcing. Proposed change: LEO Pharma proposes a BWP workshop is held to discuss this reflection paper. LEO Pharma would like to participate in such a workshop with EMA and work towards a clearer mutual understanding on biological starting materials and intermediates.	Not accepted. Based on the comments received a workshop is not deemed needed to establish a guidance document which does not introduce new regulatory requirements but instead some flexibility measures (although under more stringent conditions of overall control) proposed to introduce more flexibility.
Lines 114-117	8	Comment: With respect to the control of heparin manufacture, there is reference to the process starting at the sourcing of mucosa and later, in lines 116-117, reference is made to traceability from the slaughterhouses/abattoirs. What, if any, is the difference between the use of the terms 'sourcing of	Reasoning accepted but no impact on text.

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		mucosa' and 'traceability to the abattoir'? Does the sourcing of mucosa imply further controls in addition to the control at the abattoir? LEO Pharma considers that while traceability to the abattoir can and should be maintained with regard to the abattoir used in processing, there is limited patient safety or product quality advantage to be gained from individual pig traceability. In real terms, the more informative quality indicator is in relation to the regions used to source the porcine population. In the context of LMWH manufacture, it requires approximately 10,000 pigs to manufacture 1kg of drug product intermediate. An input of 10,000 pigs requires several abattoir sources to be used in one batch.	
Lines 115-117	4	Comment: Unclear if slaughterhouses will be required to be registered. Please clarify.	It is not required to register individual slaughterhouses. However, the manufacturer of the medicinal product has full responsibility for the material obtained from the slaughterhouses hat is used for the production of the medicinal product. In practice, a group of slaughterhouses are covered by the same Health regulation and Quality Assurance systems.
Lines 115-117	8	Comment: With reference to early stages of processing is there consideration for recognised and regulated veterinary controls that may exist in the process? Does EMA consider that the requirement to adhere to Council Directive of 26 June 964 on health problems affecting intra-Community trade in fresh meat (64/433/EEC) and EU regulation S.I. no. 434/1997:	Partly accepted. Wording will be brought in line with established wording in other guidelines. It is not the intention to provide detailed criteria for veterinary related matters.

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		European Communities (Fresh Meat Regulations, 1997) which is intrinsic to ensuring the confirmation of fitness for slaughter mitigates against the need for independent controls by the manufacturer of heparin? Proposed change: If there is the acceptance for use of other industry standards in ensuring compliance at the initial stages of sourcing, it would be beneficial for this to be stated in the reflection paper in order to provide clarity on appropriate standards.	
Line 117	4	Comment : it should be added “veterinary certificate”	Accepted.
Lines 129, 130	3	Comment: We recommend to use the terminology according to the Ph. Eur. Monograph for Plasma for Fractionation (0853): Proposed Change: Change “... obtained from either recovered or source human plasma” to “obtained from either whole blood (after separation from cellular elements) or by plasmapheresis.”	Plasma derived products will not be detailed in the document. See above comments on scope.
Lines 155, 156	3	Comment: The paper defines the term “intermediate”, however it is unclear what an “early intermediate” is. Proposed change: Include a definition of “early intermediate” compared to “intermediate”.	Accepted. Term “early intermediate” has been reconsidered as it did not sufficiently reflect the current manufacturing practice for heparins. A definition for “key” intermediate has been introduced.
Lines 156-158 & 161-162	8	Comment: In line 157, reference is made to the manufacturing process being ‘well defined’ and in line 161, reference is made to ‘full information’. Is there a guideline level of information that is required at these	Accepted.

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		earlier stages? Given the extensive downstream processing that occurs in the manufacture of biological medicinal products, is there a consideration that the detail of the early stage processing is not as critical and therefore the same level of detail is not required as later stages? Proposed change: LEO Pharma propose that the term 'full information' is removed from line 161 and is replaced by 'sufficient information given the stage of the process, with a focus on critical process parameters, traceability of supply and demonstrated MAH oversight of the process'	
Lines 159-160 161-171	6	Comment: If multiple processes are used in the early stages, the MAH should justify the use of intermediates manufactured by **variant** processes. Any differences among variant processes, e.g. additional purification / extraction step, process conditions, intermediates, material and equipment should be listed and justified for each intermediate. Greater value is added through the description of details the manufacturing process, including the *critical process parameters* for each supplier. Proposed change: It is not practical to build this request for the MAH. MAH proposes that greater value is added through the	Partly accepted. It is agreed that greater value is added through the description of details of the manufacturing process, including the critical process parameters for each supplier. However, it is not agreed that compliance to the Ph.Eur. monograph would be sufficient for a MA dossier and therefore further information of the manufacturing steps is needed and any differences thereof.

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		description of details of the manufacturing process, including the *critical process parameters* for each supplier. The comparison between each manufacturing step for each supplier does not represent added value in assuring quality of finished product because their processes are different and "proprietary". Even with different processes, the overall intent remains to obtain a purified heparin compliant with European Pharmacopeia requirements.	
Lines 161-162	4	Comment: full information may not be necessary for <u>each</u> intermediate. For intermediates identified before the "early intermediates" in the manufacturing process, limited/restricted quality attributes may be acceptable knowing that "early intermediate" is well defined and its quality control and qualification is a key step in the manufacturing process of the drug substance.	Accepted.
Lines 162 to 164	7	Comment: It is not always possible to obtain homogeneous samples of early intermediates until they have been thawed, pooled and mixed. Thus it should be clear that the Quality Attributes of the early intermediate that should characterise the manufacturing process can be based on in-process validation data of the pooled early intermediates, using intermediates from a particular supplier, and need not be determined by testing each batch of early intermediate.	Accepted. The proposed amendment of the text is agreed. However, it is noted that it is not required to characterise samples from the key intermediates to show comparability, between the various sources, on a routine basis.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Relevant Quality Attributes for each intermediate (e.g. purity profile, biological activity) should characterise the manufacturing process and should be defined by the manufacturer of the drug substance. ***Where it is not possible to determine the Quality Attributes at the stage of the early intermediate, testing for relevant Quality Attributes may be performed as early as possible, at a later stage in the manufacturing process.***	
Line 164	3	Comment: Does this also refer to the different collection and processing processes for source and recovered plasma? Information on the starting material plasma is provided in the PMF, following EMEA/CHMP/BWP/3794/03. It should be clarified that this information sufficiently describes the starting material and process of manufacturing of the plasma pools, and no further requirements are intended to be introduced via this reflection paper. Proposed change: Amend “Any differences among variant processes, e.g. additional purification/extraction step, process conditions, intermediates, materials and equipment, should be listed and justified for each intermediate.” to “Any differences among variant processes *after receipt of the starting material at the site of manufacture*, e.g.	Plasma derived products will not be detailed in the document. See above comments on scope.

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		additional purification/extraction step, process conditions, intermediates, materials and equipment, should be listed and justified for each intermediate.	
Line 164	3	Comment: “Any differences” may reflect a vast amount of information like e.g. different filter with the same qualitative characteristics etc. It should be sufficient to describe the “relevant differences” Proposed change: Replace “Any differences among variant processes…” To “All relevant differences among variant processes….”	Not accepted. All differences need to be listed and justified but not necessarily by comparability data. The level of details is exemplified in the document.
Lines 166-167	4	Comment: to add “early” Proposed change: *“Provided that the* **early** *intermediate from variant processes is sufficiently characterised,”*	Accepted. Note that the term “early intermediate” has been changed to “key intermediate”.
Line 172	3	Comment: if e.g. source and recovered plasma are considered to be derived from different sources/different manufacturing processes, this may be interpreted as the necessity to show comparability of the product for each singuidelinee plasma source. This can tie up a lot of resources and take a lot of time. It should be sufficient if the respective specifications for the intermediates and/or finished products are met. Proposed change: Amend “Thus, if a manufacturer decides to use starting materials or intermediates from	Plasma derived products will not be detailed in the document. See above comments on scope.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		different sources and / or a different manufacturing process for the early production steps it should be shown that comparable products are consistently obtained in terms of relevant quality attributes irrespective of the process applied" to "Thus, if a manufacturer decides to use starting materials or intermediates from different sources and / or a different manufacturing process for the early production steps it should be shown *that the same specifications are met or* that comparable products are consistently obtained in terms of relevant quality attributes irrespective of the process applied"	
Lines 172-175	8	Comment: In relation to the need to demonstrate comparability between products with different starting material sources or early manufacturing steps; to what extent is comparability expected and how early in the process is meant by the reference to 'early production steps'?	Partly accepted. It will be clarified what is meant by "early production steps" The document already includes guidance to the extent of the studies to support comparability (lines 178-183)
Line 173	2	Comment: comparability may also be shown at drug substance level. Proposed change:"…it should be shown that comparable drug substance/drug product is consistently obtained…."	Accepted.
Line 173	4	Comment: Clarification is needed for the term ''comparable products''. Proposed change:"…it should be shown that ~~products~~	Not accepted. See previous point.

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		comparable drug substances are consistently obtained…."	
Line 176 ff	3	Comment: this can be misinterpreted as the necessity to show quality, safety and efficacy of finished product manufactured from different sources, e.g. plasma sources. Provided the relevant specifications are met by all plasma sources, consistent quality, safety and efficacy can be assumed. Proof of comparability or lack of negative effects of different starting material sources/ manufacturing processes on the efficacy could only be proven by respective clinical studies, which would require unjustified efforts. Proposed change: rewrite line 176 ff to: Comparability should be discussed (or instead 'considered'?) taking into account the principles laid down in …..	Plasma derived products will not be detailed in the document. See above comments on scope.
Lines 176-178	6	Proposed change: For heparins, MAH would like to have no clinical studies to manage for all products which are compliant with the European Pharmacopeia monograph.	Partly accepted. The aim of the comparability request is not to have clinical studies. However, as indicated in the document "Discernable differences in quality attributes should be discussed and justified in terms of product quality (e.g. product heterogeneity) as well as safety (including virus safety) and efficacy of the finished product."
Lines 183-184	6	Any storage periods for intermediates should be set and justified by stability data. In MAH point of view, such stabilities do not represent added value because intermediates are not stored.	Not accepted. Request for stability data can be ignored if not applicable for certain products.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 183-184	4	Comment: to add “and conditions” Proposed change: “Any storage periods and conditions for intermediates should be set and justified by stability data.	Accepted.
Line 188	4	Comment: Is supplier the mucosa supplier, or perhaps the crude supplier? Please clarify.	Not accepted. Could be both.
Line 188	4	Comment: Suggest a table defining what GMP measures are expected at the various stages as in ICH Q7	Not accepted. Reference is made to Annex 2.
Lines 188 to 193	7	Comment: The respective GMP responsibilities of the early intermediate manufacturer and the drug substance manufacturer should be clearly defined. Proposed change: GMP measures (e.g. contract between supplier and manufacturer of medicinal product, audit system) should be adequate to ensure an appropriate control while allowing sourcing of starting materials or early intermediate biological products in different locations from third countries. ***Respective GMP responsibilities should be clearly defined in a Quality Agreement.*** Reference is made to Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use Annex 2: Manufacture of Biological Medicinal Substances and Products for Human, Part B.	Partly accepted. Document will be amended to clarify the GMP related matters. However, it is not the intention of the document to provide detailed guidance on GMP matters.
Line 190	2	See introduction: define "third countries".	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 190	4	Comment: Clarification is needed for the term "different locations from third countries". We recommend changing the sentence by giving a clear description of what is meant with "third countries'. Proposed change: " different locations ~~from third~~ in countries that are not members of the European Union	Partly accepted. Text will be amended to clarify what is meant with “different locations.” It is not the intention to distinguish IN versus OUTSIDE EU sourcing.