27 June 2024

Submission of comments on 'Guideline on the clinical investigation of recombinant and human plasma-derived factor IX products (draft 15 November 2018) (EMA/CHMP/BPWP/144552/2009 rev. 2)

Name of organisation or individual
- Catalyst Biosciences - International Plasma and Fractionation Association (IPFA) – no comments - Novo Nordisk A/S - Plasma Protein Therapeutics Association (PPTA) on behalf of member companies BioProducts Laboratory, Biotest, CSL Behring, Grifols, Kedrion and Takeda - SANOFI

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1. General comments

Stakeholder number	General comment	Outcome (if applicable)
Catalyst Biosciences	The stakeholder commends EMA for removing the requirement for studying previously untreated patients (PUPs) from the guidance document, however we would like to point out that for any modified FIX molecule such as dalcinonacog alfa (Recombinant human factor IX protein modified with three point mutations) no patients have been previously exposed to the molecule so all individuals will be PUPs. The guidance document provides for instructions for the development of intravenous replacement factor, of which only generic agents may be developed in the future, but does not appear to provide guidance for the development of other presentations such as subcutaneous agents for prophylaxis that are not designed to treat on demand bleeding. Subcutaneous administration of FIX is the future for FIX and other clotting factor replacement. Similarly, gene therapy guidance is not provided. To ensure that the guidance is current when it is finalized, the stakeholder respectfully suggests that specific guidance for subcutaneous agents be provided, especially a focus on minimum steady-state activity levels or trough activity levels. With prolonged time to maximal concentration and redosing before that time, pharmacokinetic studies do not disclose the properties of subcutaneously administered agents as multiple doses lead to a summation of activity levels and high steady-state levels, while single doses may result in barely detectable increases in blood activity levels. Further, continuous infusion guidance will not apply to subcutaneously administered agents.	The stakeholder comments are well acknowledged, but the proposal that specific guidance for subcutaneous agents be provided is not agreed at this stage. Please consider the following points: - A PUP is defined as follows in the EMA FIX Clinical Investigation Guideline Section 4.5 (previously section 6.4): *Previously untreated patients (PUPs) are defined as those patients who have never been treated with clotting factor products (except previous exposure to blood components).* Therefore, treatment switchers would not be considered as PUPs. - There is insufficient evidence whether subcutaneous administration of FIX is the future for replacement therapy. - This guideline is intentionally not applicable for Haemophilia gene therapy and non-replacement therapies. Separate guidance for ATMPs are in place or might be developed in the future. - Due to insufficient experience with subcutaneous administration of clotting factors in haemophilia, detailed guidance cannot be implemented in the guideline for such products. However, this might be changed in the future. Currently, basic concepts of this guideline may also be applicable for subcutaneously administered clotting factors,

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		whereas specific recommendations on the PK is not applicable.
Novo Nordisk A/S	Novo Nordisk appreciates the removal of the obligation to perform clinical trials in PUPs for marketing authorisation purposes and that a core parameter set for registry data collection in haemophilia have been introduced. However, in finalising the guideline we suggest developing this approach even further and to focus on registries in the post-marketing phase (please see specific comment). Furthermore, the draft guideline would benefit from further clarity in the Risk Management Plan section regarding the post-marketing investigation applying both non-interventional post-approval commitment studies *and* registries. It seems to be challenging to have both given the rare population and it should be considered if it is necessary for factor IX replacement products to apply both for collecting data (please see specific comment).	At the current stage, no further changes of the requirements for clinical investigation of FIX products are foreseen. The stakeholder is referred to the EMA "Guideline on registry-based studies" (https://www.ema.europa.eu/en/guideline-registry-based-studies).
PPTA	Please clarify if a registry included in the Risk Management Plan for Factor IX products should be managed according to GVP modules V & XVI or if it should be considered as a PASS and therefore managed in accordance with GVP Module VIII.	Pharmacovigilance requirements as stated in GVP modules apply as for any other products. Specific requirements for FIX products are given in this guideline.
PPTA	The guideline seems to extend the expectation of post-marketing registries. The trade-off is that the hard-to-find Previously Untreated Patients (PUPs) are no longer a requirement for the pre-approval pivotal clinical studies, which is laudable. However, the burden of subject numbers has not changed. This will impact manufacturers/MAA if there were to be a new factor IX clinical trial planned, or a major manufacturing change to a factor IX product that was so significant as to unavoidably need another clinical trial.	The stakeholder comments are acknowledged. Concerns regarding the burden of subject numbers in clinical trials investigating treatment options in haemophilia B are acknowledged as well. However, this number has been selected by balancing the clinical data package needed to demonstrate efficacy and safety against the availability of patients suffering from a rare disease. The number of patients is expected to be adequate to provide relevant information on general safety aspects and to

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		demonstrate efficacy of a factor IX product in terms of its ability to restore factor IX levels and reach haemostasis, to stop as well as to prevent bleeding. In view of the limited number of patients in the pre-authorisation trials, further information mainly focussing on safety aspects is needed through post-marketing investigations in registries. Of note, the removal of the requirement of PUP studies generally reduces recruitment burden in the clinical trials.
PPTA	Participation in clinical trials of patients previously treated with plasma-derived product and then switched to recombinant product and vice versa should be discussed.	Not agreed. This issue is outside the scope of this GL. Of note, the value of investigating factor-switching, especially in clinical trials in the context of a marketing authorisation, remains largely elusive.
SANOFI	Sanofi welcomes the opportunity given by the EMA to comment on the draft revision guideline on clinical investigation of recombinant and human plasma-derived factor IX products. We agree with the use of registries rather than PUPs studies. It would be helpful to clarify how long registry data are expected to be collected. Details on line 573ff on treatment may be burdensome to collect for many years. It would be helpful for the guideline to clarify whether the use of registries also applies to non-replacement products. Will MAHs receive guidance regarding the registry requirement in relation to the PIP? Comment: treatment status PUP/PTP	a) The stakeholder concerns on the burdensome of collecting registry data are acknowledged. The proposed core data set is based on a broad consensus of different stakeholders. In order to complement clinical trial data, especially in PUPs, and to improve the future benefit-risk evaluation of haemophilia therapies, it is considered a reasonable and feasible compromise to collect these register data. b) The proposal on clarification that use of a registry could also apply for non-replacement products is agreed (see specific comment below).

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	A concept of minimally treated patients should be defined by the guideline including how this patient group can be useful in the evaluation of inhibitor development. Per the current guideline, PUPs are defined as "those patients who have never been treated with clotting factor products (except previous exposure to blood components) [lines 394-395]. PUPs are much rarer than minimally treated patients. The guidelines should clarify whether minimally treated patients could also be considered to meet the registry requirement for new products.	c) No guidance regarding how long registry data should be collected can be made at this stage. This will be further evaluated in PSUR assessment. Non-replacement products are not within the scope of this guideline. d) The definition of PUPs is already defined in the guideline and it is clearly outlined in the guideline why data in PTPs are required.

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
104	Catalyst Biosciences	Since this guidance applies to intravenous agents suggest insert "intravenous" unless the guidance is adapted to cover subcutaneous and gene therapy as well. Proposed change (if any): This guideline describes the clinical trials required for authorisation with respect to human plasma-derived and recombinant factor IX products, including, but not limited to: Intravenous, Subcutaneous, and Gene Therapy presentations.	Agreed. Section 1. Introduction refers now to IV administration. Additionally, it is clarified that *"currently there is insufficient experience with other routes of administration of a coagulation factor to provide general guidance"*. Although it is noted that some aspects of the guideline might also be applicable for other routes of administration. Gene therapy products and non-replacement therapies are outside the scope of the guideline.
115	Catalyst Biosciences	Ideally EMA should broaden the applicability of the guidance by including desired blood activity levels achieved after dosing. If these are not incorporated in the guidance, then text should add "subcutaneous administration to the recommendation that scientific advice be sought. Proposed change (if any): "If a specific benefit of a certain product should be claimed e.g. a prolonged half-life or subcutaneous dosing which might lead to modifications of the clinical trial, it is recommended that advice on the design of clinical studies is sought via an EMA scientific advice procedure."	Partly agreed. - Target blood activity levels are beyond the scope of this GL and are rather in the scope of clinical treatment GLs. The following change has been implemented: - If product specific characteristics may require a modification of the clinical trial design (e.g. a prolonged half-life or subcutaneous dosing); it is recommended to seek advice via an EMA scientific advice procedure.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
155	Catalyst Biosciences	Most intravenous pharmacokinetic parameters do not apply to subcutaneously administered agents with prolonged time to maximal concentration. The duration of maintaining elevated activity levels post dosing is important for extended half-life agents. Proposed change (if any): "Appropriate pharmacokinetic data (incremental recovery, half-life, area under the curve (AUC), clearance and trough activity levels (at 72 and 168 hours) are the most important surrogate endpoints for efficacy of a new factor IX product.	Not agreed. Non-intravenously administered products are currently not within the scope of this guideline. In addition, no recommendations can be made which trough levels are necessary as this rather relates to individual treatment goals and this is outside the scope of the GL. For (non-)clinical investigations to be conducted pre- and post-authorisation for subcutaneous products, it is recommended that advice be sought via an EMA scientific advice procedure.
158	Catalyst Biosciences	The duration of total exposure to be studied, beyond exposure days should be specified for extended-half-life and frequently administered subcutaneous agents (for example daily administration). The stakeholder suggests 6 months of exposure in concordance with line 321. Proposed change (if any): Furthermore, clinical efficacy of factor IX treatment (e.g. prophylaxis, on demand) should be assessed during a period of a minimum of 50 exposure days and a period of 6 months by the patients themselves and treating physicians.	Not agreed. Non-intravenously administered products are currently not within the scope of this guideline. For (non-)clinical investigations to be conducted pre- and post-authorisation for subcutaneous products, it is recommended that advice be sought via an EMA scientific advice procedure.
207	Catalyst Biosciences	Neutralizing antibodies to modified FIX molecules such as dalcinonacog alfa (Recombinant human factor IX protein modified with three point mutations) may not neutralize wild-type FIX so should not be termed "inhibitors". The rate of development of neutralizing antibodies should be determined and whether these are	Not agreed. Within the scope of this revision, the requirement for clinical PUP studies for marketing authorisation purposes will be deleted. Therefore, studies

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		also inhibitors to wild-type FIX. Since no patients have been previously exposed to modified FIX molecules, all individuals will be PUPs and the rate of neutralizing antibodies should be compared with the rate of inhibitors in PUPs treated with wild-type FIX (>10%). Proposed change (if any): Insert text: The rate of development of neutralizing antibodies should be determined and whether these are also inhibitors to wild-type FIX.	investigating the occurrence of FIX inhibitors and anti-drug antibodies are only to be conducted in PTPs, for the purpose of marketing authorisation. The incidence of inhibitors is much less in PTPs with Haemophilia B compared to Haemophilia A and compared to the respective PUPs. Therefore, no specific guidance is made regarding the distinction between inhibitors and FIX-WT antibodies. However, analysis of any cross-reactivity of neutralising antibodies is endorsed. Of note, the definition of previously untreated patients does not generally refer to the exposition of a certain unmodified or modified factor product. There is also insufficient evidence that product switching could have an impact on the risk and time course of inhibitor development.
283	Catalyst Biosciences	Pharmacokinetic studies do not disclose the properties of subcutaneously administered agents as multiple doses lead to a summation of activity levels with the potential to achieve therapeutic steady-state levels, while single doses may result in barely detectable increases in blood activity levels. Proposed change (if any): Specify that the pharmacokinetic section does not apply to subcutaneously administered agents.	Not agreed. Please see changes made in the introductory section *"currently there is insufficient experience with other routes of administration of a coagulation factor to provide general guidance"*.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
296	Catalyst Biosciences	Pharmacokinetic studies do not disclose the properties of subcutaneously administered agents as multiple doses lead to a summation of activity levels with the potential to achieve therapeutic high steady-state levels, while single doses may result in barely detectable increases in blood activity levels. The stakeholder suggests that appropriate text be added for subcutaneously administered agents. Trough level stability over time should substitute for repeat pharmacokinetic studies (retest at 3-6 months) Proposed change (if any): Insert text: For subcutaneously administered agents, trough levels prior to the next administration should be obtained. Retest at monthly intervals for 6 months.	Not agreed. Please see above.
326	Catalyst Biosciences	Continuous infusion studies do not apply to subcutaneously administered agents. Proposed change (if any): Insert text: Continuous infusion studies do not apply to subcutaneously administered agents.	Not agreed. Please see above.
344	Catalyst Biosciences	Regularly administered subcutaneous agents may take many days (>20 days) to reach steady-state and have prolonged periods for clearance (>20 days) should not be discontinued for washout to repeat pharmacokinetics. Trough levels after achieving steady-state should be obtained prior to the next scheduled dose.	Not agreed. Please see above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Insert text: Regularly administered subcutaneous agents that may take many days to reach steady-state and have prolonged periods for clearance and should not be discontinued for a washout to repeat pharmacokinetics. Trough levels should be obtained prior to a scheduled administration, at monthly intervals.	
348	Catalyst Biosciences	Given the prolonged period required to washout subcutaneously administered FIX, inhibitor titres should be determined using heat treatment in the Bethesda assay. Proposed change (if any): The titre of the inhibitor should be reported in Bethesda Units (BU) using the heat-treated Bethesda assay or the heat-treated Nijmegen modification of the Bethesda assay.	Not agreed. For clinical investigations to be conducted pre- and post-authorisation for subcutaneous products, including inhibitor-monitoring related issues, it is recommended that advice be sought via an EMA scientific advice procedure.
Annex II PTP ≥12y study	Catalyst Biosciences	Footnote 2 does not apply to switch to subcutaneous agent. Pharmacokinetic parameters: Incremental recovery, half-life, AUC, clearance, may not apply to a single subcutaneous dose. For extended half-life and frequently dosed subcutaneously administered agents, activity level at 72 and 168 hours is more appropriate. Repeating pharmacokinetics at 3-6 months is inappropriate for agents with extremely prolonged half-life or designed for repeated administration to reach steady-state levels Proposed change (if any): Add text: activity levels at 72 and 168 hours, as appropriate.	Not agreed. Please see above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Insert text: For subcutaneously administered agents, trough levels prior to the next administration should be obtained. Retest at monthly intervals for 6 months.	
Annex II Children <12y study	Catalyst Biosciences	Pharmacokinetic parameters: Incremental recovery, half-life, AUC, clearance, may not apply to a single subcutaneous dose. For extended half-life and frequently dosed subcutaneously administered agents, activity level at 72 and 168 hours is more appropriate. Proposed change (if any): Add text: activity levels at 72 and 168 hours, as appropriate.	Not agreed. Please see above.
Annex II Children <12y study	Catalyst Biosciences	Immunogenicity: 50 exposure days may be too brief Proposed change (if any): Insert text: Continue until a minimum of 6 months or 50 exposure days.	Not agreed. The recommendation to monitor immunogenicity for a minimum of 50 exposure days is valid for intravenously administered products. For subcutaneous products or non-replacements products different concepts may apply. As there is currently insufficient evidence to make clear recommendations for such products, advice should be sought via an EMA scientific advice procedure.
206	Novo Nordisk A/S	*"Inhibitors of factor IX have been demonstrated in approximately 4% of patients with severe haemophilia B."*	Partly agreed.

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		Please consider the inhibitor rate of 4%, as new data show a higher inhibitor rate in haemophilia B. The reported range lies within 5–14%. NN Proposal: Please consider to update the inhibitor rate according to below references: 1) Franchini, M., et al. (2016). "Inhibitor incidence in previously untreated patients with severe haemophilia B: a systematic literature review." Thromb Haemost 116(1): 201-203. 2) Van Den Berg, M et al. Inhibitor incidence in PUPs with severe haemophilia B is higher than usually reported; data from the PedNet registry. Haemophilia, 24 pg. 23-31. 2018. http://dx.doi.org/10.1111/hae.13392. 3) Inhibitor development in haemophilia according to concentrate. Four-year results from the European HAemophilia Safety Surveillance (EUHASS) project." Thromb Haemost 113(5): 968-975. However, up to 19% has been reported: 4) A., M., et al. (2016). "Mutation analysis of Swedish haemophilia B families – high frequency of unique mutations." Haemophilia 22(3): 440-445. NN suggests: Inhibitors to factor IX have been demonstrated in approximately 5-14% of patients with severe haemophilia B.	There is notable heterogeneity in the reported inhibitor incidence rates in Haemophilia B subjects To avoid any possible misinterpretations, the guideline now no longer gives a specific incidence rate of inhibitors.

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475	Novo Nordisk A/S	*"Incremental recovery is determined as the peak level recorded 30 minutes after infusion and reported as [IU/ml]/ [IU/kg]."* The definition of incremental recovery is not precise. **NN Suggests** rephrasing to: "Incremental recovery is defined as the increase in plasma factor activity per IU/kg of factor administered and reported as [IU/ml]/ [IU/kg]."	Agreed. Within Section 6.2, it is now stated that "Incremental recovery is defined as the increase in plasma factor activity in IU/ml per IU/kg of factor administered and reported as [IU/ml]/ [IU/kg]. Incremental recovery is determined by using the peak factor level recorded in the first hour after infusion." To avoid redundancy, the respective sentence has been deleted from Section 7.2.
485	Novo Nordisk A/S	"*8. Risk Management Plan*" The requirement in the Risk Management Plan to have post-marketing investigation applying both non-interventional post-approval commitment studies and registries seems to be challenging given the rare population and it should be considered if it is necessary for factor IX replacement products to apply both ways of collecting data. Historically, it has proven to be difficult to recruit patients to non-interventional post-marketing studies which poses only minor incentive to both Health Care Professionals and PUP/PTPs. Given the limited access to patients, Novo Nordisk suggests focusing on registries only in the post-marketing investigation and that data should be collected in registries that needs to develop a Standard	Concerns regarding the burden of subject numbers in clinical trials investigating treatment options in haemophilia B are acknowledged. However, this number has been selected by balancing the clinical data package needed to demonstrate efficacy and safety against the availability of patients suffering from a rare disease. The planning of register-based studies in the context of post-marketing investigations is a very important topic on which the EMA has taken substantial initiatives. The stakeholder is referred to EMA guideline on registry-based studies for further guidance (https://www.ema.europa.eu/en/guideline-registry-based-studies).

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		Core Data Set which addresses the specific needs for new products and can be used for regulatory purposes.	
502	Novo Nordisk A/S	As part of the Risk Management Plan specific data is requested in case of inhibitor formation. It is unclear what is meant with 'intermittent inhibitor'. If it is the same as a transient inhibitor, then please clarify this, and please define what is meant by an intermittent/transient inhibitor. NN suggests: For clarity and transparency, please clarify exactly what is understood by "intermittent inhibitor"	Agreed. Transient inhibitors are usually defined as those disappearing spontaneously within a shorter period of time (within 6 months), while remaining on standard treatment and without the use of immune tolerance induction therapy. This is now clarified in Section 8. RMP.
506	Novo Nordisk A/S	As part of the Risk Management Plan specific data is requested in case of inhibitor formation. It is unclear what is meant with "Type 1 and type 2 inhibitors". NN Suggests: Please clarify and/or define what is meant by "Type 1 and type 2 inhibitors" and consider if this information is relevant for the Risk Management Plan.	Partly agreed. The terms "Type 1" and "Type 2" inhibitors generally refer to the kinetics of factor inactivation and completeness of inactivation. Due to their uncommon use in the context of FIX, the terms are deleted.
Annex II, throughout page	PPTA	Comment – see in general comments The burden of subject numbers has not changed. This will impact manufacturers/MAA if there were to be a new factor IX clinical trial planned, or a major manufacturing change to a factor IX product that was so significant as to unavoidably need another clinical trial.	The comment is acknowledged.

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		Proposed change (if any):	
Lines 245-252 (page 8)	PPTA	Comment: Text does not represent what is in Annex I – Overview on clinical trial concept. Proposed change (if any) Information provided in Annex I should be comprehensively discussed in the main text.	Not agreed. The Section has been reviewed. Of note, only general aspects of the clinical trial concept are presented in Section 6.1 now under section 4. The second paragraph of this section mainly refers on the age-staggered approach. I.e., only the following key points are mentioned in this section: - The overall minimum number of subjects from pre-authorisation clinical trials is 40. - The initial evaluation should be conducted in 12 PTPs (≥12years, PK + S). - After 10 PTPs (from an overall of 20 PTPs ≥12years) have been evaluated for PK + E + S (50 EDs), clinical trials in the younger age cohorts should be started.
Lines 248-249 (page 8)	PPTA	Comment: Inconsistency with patient numbers; this also contradicts to information in section '6.2 Efficacy in PPTs>12 years: page 9, lines 284': ··· "Subsequently, when PK and efficacy/safety in 10 PTPs ⩾12 years' for at least 50 EDs are available, the clinical trial(s) in children 0 - <12 years can be initiated." ···	Not agreed. The Section has been reviewed. Of note, initial PK + S data should be obtained in 12 PTPs (≥ 12 years), as detailed in Section 6.1, 6.2, and Annex II. These data should be supplemented by an additional 8 PTPs of the same age cohort to provide overall E+S data from 20 PTPs (≥ 12 years). After availability of

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		Proposed change (if any): Please clarify/ correct patient numbers; **Annex II also mentions 12 patients.**	S (+E) data of 10 out of 20 PTPs (≥ 12 years) treated for 50 EDs, clinical investigation in children <12 years should be started.
Line 284 (page 9)	PPTA	Comment: Inconsistency with patient numbers; this also contradicts to information in section 6.1 (lines 248-249, see comment above). "A pharmacokinetic trial, should be performed in at least 12 PTPs (>150 exposure days (EDs)) suffering from haemophilia B (factor IX ≤2%) and who are immunocompetent (HIV patients should have CD4> 285 200/µL)." Proposed change (if any): Please clarify/correct patient numbers; **Annex II also mentions 12 patients.**	Not agreed. Please see above.
Line 296 -297 (page 9)	PPTA	Comment: "At least 3 different lots should be employed in the trial.' Proposed change (if any): Please clarify if this means that 4 patients (3 groups) will receive the same lot?	Agreed. This has been removed.
Line 305-307 (page 10)	PPTA	Comment: …"Patients taking part in the pharmacokinetic trial should continue treatment with the product, and should be re-tested for the same pharmacokinetic parameters after 3-6 months using the same dose as in the first investigation." …	Agreed that this is no longer required. This requirement has been removed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): What is the scientific justification of re-testing after 3-6 months? (Scientific justification should be given)	
Lines 306-307 (page 10)	PPTA	Comment: " … see **Annex III** for further details."… Proposed change (if any) This is not correct – this should be **Annex II**	Agreed. The reference has been corrected as proposed.
Line 312 (page 10)	PPTA	Comment: Efficacy including surgery Proposed change (if any): Reference to Annex II should be made. The statement above should be included in Annex II.	Agreed. Reference has been made to Annex II as proposed.
Lines 313-315 (page 10)	PPTA	Comment: …"Clinical efficacy of factor IX should be evaluated in at least 20 PTPs (≥12 years, >150 EDs), suffering from haemophilia B (factor IX ≤2%) and who are immunocompetent (HIV patients should have CD4 > 314 200/µL)." Proposed change (if any): Clarification is needed whether a group of 20 PTP patients may include 5 patients which undergo surgeries and 12 patients who will be treated with aim of PK study or it should be separate groups of patients.	Not agreed. As stated in Section 6.1 (now section 4) "*general aspects on clinical trials*" the overall number of patients typically to be enrolled in pre-authorisation trials is a minimum of 40. This implies by intention that the minimum of 12 patients evaluated for PK as well as the minimum of 5 patients undergoing at least 10 surgical procedures can be part of this population.

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			In Section 6.2 (PK subsection) it is further stated that patients taking part in the pharmacokinetic trial should continue treatment with the product. This usually is done within a pivotal clinical trial. Likewise, surgical procedures are evaluated within the initial population of 40 PTPs.
Lines 326 and ff. (page 10)	PPTA	Comment: Section 'Continuous infusion' This section describes assessment of continuous infusion in patients with severe haemophilia B undergoing elective surgery: "If continuous infusion therapy is claimed, the study should be carried out in at least 10 severe haemophilia B patients (FIX ⩽2%) undergoing elective major surgical procedures." Proposed change (if any): This should be reflected in the title of this section: "Continuous infusion in major surgeries". Consideration should be given to include information about continuous infusion into Annex II.	Not agreed. The title and associated section are considered sufficiently clear and also in line with the EMA FVIII guideline.
Lines 359 and ff.	PPTA	Comment: Section '6.3. Clinical investigation in children <12 years' Proposed change (if any): This is the most vulnerable age population. Clear division similar to 6.2 Section is recommended, such as choice of patients; pharmacokinetics; clinical efficacy and inhibitor testing. Reference to Annex II should be made in corresponding place.	Agreed. As proposed, subsections are introduced analogous to Section 6.2. (now section 4.3). In addition, reference to Annex II has been included.
Line 400-401	PPTA	Comment:	Agreed.

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(page 12), throughout document		Risk Management Plan Proposed change (if any) Provide abbreviation "RMP" when first mentioned in line 400-401, and then use through the text or not use abbreviation at all. See also page 14, line 491. Consistency is needed through the text.	The proposed changes have been made.
113	SANOFI	If the use of a registry applies to non-replacement products, suggest adding "registry" to the examples in parentheses.	Non-replacement therapies are not in the scope of the guideline.
543-545	SANOFI	Comment: The registry requirement appears to be intended for all new products, i.e. those without a clinical study in PUPs. Proposed change: For new products, i.e. those without clinical data on PUPs, it is crucial to identify and mitigate new safety issues that might emerge once a product is on the market.	Partly agreed. The registry requirement is intended for all new FIX products. In general, this is irrespective of whether these are identified as novel and irrespective of the extent of available PUP data.
563ff	SANOFI	Regarding the capture of treatment information for patients on routine prophylaxis, the level of detail should be clarified as patients are dosing themselves regularly at home. We would not expect that patients enters information in a registry at each dose. Dose information should preferably be structured as prescribed dose per injection and frequency of injection. We recommend that the date of initiation of prophylaxis and regimen (dose and frequency) be captured, as well as any changes in regimen (date of change and dose/frequency of dosing of new regimen). Episodic and surgery	Not agreed. The recommended core data set is based on a broad consensus of different stakeholders and it should be noted that it should be used for data collection in PUPs primarily albeit the data set is also applicable for PTPs (please be also referred to the EMA report on the 2018 Haemophilia registries Workshop

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		dosing in these patients would be captures in detail as specified in Lines 574-584. Rationale: The current wording implies that treatment information (date, weight, etc) should be captured for every prophylactic dose for each patient, which is very burdensome. Capturing prophylactic dosing information more concisely is more feasible and provides the desired information.	https://www.ema.europa.eu/en/events/haemophilia-registries-workshop). Further guidance on registry-based data capturing is beyond the scope of this guideline. Of note, in order to account for the burden of data capturing, some disease registry already have technical measures in place, e.g. detailed data (single treatment data) are to be provided for the first 100 EDs and after that cumulated treatment data could be provided.