21 May 2015
EMA/CHMP/BPWP/111667/2015
Committee for medicinal products for human use (CHMP)

Overview of comments received on 'Draft Guideline on clinical investigation of recombinant and human plasma-derived factor IX products' (EMA/CHMP/BPWP/144552/2009 rev. 1)

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

Stakeholder no.	Name of organisation or individual
1	Biogen Idec
2	International Plasma Fractionation Association (IPFA)
3	Plasma Protein Therapeutics Association (PPTA)
4	NDA Regulatory Science

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
4	This could have been a good opportunity to include other forms of therapy for Factor IX deficiency such as Gene Therapy which is of significant current interest. The similarities and differences in the approach to different modalities would help developers of different modalities of therapy. It is suggested that the link between potency assays and efficacy/ safety/ benefit:risk is exemplified based on experience so far. For example, would the same assay be sufficient for predicting lack of efficacy and thrombotic risk? Should the antibodies (inhibitors) be further characterised e.g., neutralising vs. binding etc?	This guideline specifically addresses Factor IX products. Scientific advice/protocol assistance can be requested for other forms of therapy (e.g. gene therapy). Concerning the link between potency assays and efficacy/safety benefit:risk, a more detailed Question and Answer document is in development to provide further information on the new aspects included in this guideline revision. Concerning antibodies (inhibitors), please refer to the guideline; there are no changes on this aspect with this rapid revision.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
235-252	2	Comment: IPFA would like to receive confirmation that this additional information will not be required by national authorities on the occasion of new waves for MRP or DCP procedures for already registered products, nor unmodified FIX products.	The revised wording is based on experience from the development of recombinant FIX proteins and modified recombinant FIX proteins (see workshop reports for further details) and might not be applicable for products already authorised via MRP or DCP.
249	1	Comment: Comparability between potency labelling and in vivo functionality does not exist for current licensed products as exemplified by the different in vivo recovery (and by inference different efficacy) for recombinant FIX vs. plasma derived FIX when dosed at equivalent units (see lines 88-91). It should only be necessary to conduct comparability of potency against an appropriate licensed product. Proposed change: Amend '…comparability (with the unitage applied) to existing licensed products based on comparisons of *in vitro…*' to '…comparability (with the unitage applied) to an appropriate ~~existing~~ licensed product~~s~~ based on comparisons of *in vitro…*'	Partly accepted. Proposed wording has been introduced, however slightly modified.
250-251	1	Comment: The physicians and laboratories need to be aware of the risk of underestimating potency due to variability associated with the different assays, while for the end user (or patient) this is less important. The product	Not accepted. Core SmPC already includes a statement; however guidance will be a case by case approach to be addressed individually. Current wording is considered appropriate.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		information is considered to be the most appropriate primary source of information on this issue, and as noted in Line 525 additional educational material could supplement this. Proposed change: '…and *in vivo* functionality. "Discrepancies observed in potency between assays and the ~~C~~consequences for laboratory monitoring of product plasma levels should be addressed in the risk management plan where necessary, and appropriate guidance ~~information~~ should be given in the product information ~~to users of the product~~.'	
262-266	1	Comment: The sampling schedules currently proposed in the guidance seems a little excessive, especially in the initial phase. While it might be worthwhile to collect extra samples in the initial distribution phase in the earlier trials to get a proper characterization of the PK, it is reasonable to expect that we can take fewer samples in later trials and still get an adequate description of the PK. It is recommended that sampling times are not specified in this guideline and that relevant pharmacokinetic guidelines should be followed. Proposed change: ~~'Samples should be taken before 262 injection of 50-75 IU/kg of the factor IX product (baseline), 10-15 minutes (times refer to the interval 263~~	Not accepted. The sampling schedule is in accordance with ISTH recommendations. Current wording already allows for adjustment depending on the activity time profile (e.g. for prolonged half-life products). In order to enable comparison of PK-profiles by regulatory authorities, the recommendation of sampling time points will be maintained.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~after the completion of the infusion) and at 30 minutes, and 1 hour. Additional time points to include 3, 264 6, 9, 24, 48, and 50 hours post-infusion; a 72 hour sample is optional provided the patient was given 265 at least 75 IU/kg.~~ Appropriate timepoints for samples should be selected to adequately characterize the PK and to calculate relevant PK parameters such as Cmax, AUC and t1/2'.	
270-271	1	Comment: Generally, "the same assay" cannot be used for potency labelling and clinical monitoring due to different assay set-up, range and sensitivity requirements. In the spirit of the ISTH recommendations, pharmacokinetic studies should employ the most appropriate assay; one that has been optimized and fully validated for accuracy, precision and linearity throughout the required assay range, whether this is a chromogenic or clotting method. Proposed change: '…be described. ~~Preferably the same assay should be used for analysis of the product and the patient's plasma (see also 6.1.1).~~'	Not accepted The principle to use the same assay for labelling as well as for monitoring of patient plasma samples should remain. The term "preferably" allows flexibility; therefore the current wording will be maintained.
274-275	3	Comment: over the past years some evidence has emerged that indeed PK may show variations according to body weight. In that respect, the proposal reflects scientific standard. There is, however, a slight caveat: given the rarity of haemophilia B, and	Comment acknowledged.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		consequently the small sample sizes in clinical trials, the interpretation of such data is hampered. Such information would need to be updated after each trial, including post-licensure safety studies. Even though, it will remain questionable in how far weight-dependent PK data will allow comparison between products, given different population characteristics (e.g., age and weight distribution). It has also to be assumed that data may vary according to geography (different mean body weight of populations in US, versus e.g. Comment (cont): Europe, or Asia).	
315-316	1	Comment: Inhibitor formation generally occurs within 40 EDs. As haemophilia B is a rare disease, allowing subjects with 100 prior EDs rather than 150 EDs is reasonable. Proposed change: 'Previously treated patients (PTPs) with at least ~~150~~ 100 treatment EDs to previous products are considered as low risk patients and should be evaluated for product related immunogenicity.'	Not accepted. This comment is not within the scope of this rapid guideline revision and would need a broad and substantial debate. For the time being the current definition of PTP will be maintained.
324 - 327	1	Comment: Drug interference in the inhibitor assay may be minimized by particular sample pre-treatment steps such as heat-inactivation or physical removal of residual FIX protein to allow for shorter washout periods. Proposed change: '……it is proposed to perform sampling for inhibitor	Not accepted This comment is not related to the modifications proposed. Current wording will be maintained.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		measurements not less than 3 days after the previous administration, if possible, unless lack of interference by residual factor IX product can be demonstrated during assay validation.'	
351-353	1	Comment: The sampling schedules currently proposed in the guidance seems a little excessive, especially in the initial phase. While it might be worthwhile to collect extra samples in the initial distribution phase in the earlier trials to get a proper characterization of the PK, it is reasonable to expect that we can take fewer samples in later trials and still get an adequate description of the PK. It is recommended that sampling times are not specified in this guideline and that relevant pharmacokinetic guidelines should be followed. Proposed change: ' With regard to patient compliance, PK sampling time points can be reduced to measurements prior to infusion (baseline) and ~~1 hour, 10 hours, 24 hours and 48 hours after infusion~~. Appropriate timepoints for samples should be selected to adequately characterize the PK and to calculate relevant PK parameters such as Cmax, AUC and t1/2.'	Not accepted See above
398-401	1	Comment: Detailed patient diaries or a logbook may not be standard in all geographies/centres, so it may not be possible to obtain this documentation for patients.	Not accepted This comment is not related to the modifications proposed. Current wording will be maintained.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change '…marketed. ~~A detailed patient documentation (diary, logbook etc.) covering the last 50 exposure days or 399 the last 2 years per patient to confirm treatment modality (i.e. prophylaxis, on demand or recent 400 surgery) is needed as a prerequisite for patient enrolment and should be available upon request.~~ Before enrolment, it should be established that the patient has previously been treated for at least 50 exposure days or the last 2 years. Patients with severe haemophilia...'	
456-460	1	Comment: The sampling schedules currently proposed in the guidance seems a little excessive, especially in the initial phase. While it might be worthwhile to collect extra samples in the initial distribution phase in the earlier trials to get a proper characterization of the PK, it is reasonable to expect that we can take fewer samples in later trials and still get an adequate description of the PK. It is recommended that sampling times are not specified in this guideline and that relevant pharmacokinetic guidelines should be followed. Proposed change: '~~Samples should 456 be taken before injection of 50-75 IU/kg of the factor IX product (baseline), 10-15 minutes (times 457 refer to the interval after the completion of the infusion) and at 30 minutes, and 1~~	Not accepted See above

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~hour. Additional 458 time points to include 3, 6, 9, 24, 48, and 50 hours post-infusion; a 72 hour sample is optional 459 provided the patient was given at least 75IU/kg. Depending on the type of factor IX product (e.g. 460 prolonged half-life) further sampling time points could be necessary~~. Appropriate timepoints for samples should be selected to adequately characterize the PK and to calculate relevant PK parameters such as Cmax, AUC and t1/2'	
522	1	Comment: It would be helpful to reword the sentence for clarity. Proposed change: 'The measurement of ~~Plasma~~ plasma factor IX levels can be significantly affected by the assay used for clinical monitoring.'	Accepted. (Note this is a sub-heading.)
522	2	Comment: misprint: "Plasma factor IX levels significantly affected by assay used for clinical monitoring" Proposed change (if any): add "can be": "Plasma factor IX levels can be significantly affected by the assay used for clinical monitoring"	Partly accepted. See above.
525-527	1	Comment: Assay discrepancies should be included in the risk management plan only if warranted. Proposed change: 'The Risk Management Plan ~~is~~ may be an appropriate	Not accepted. See above

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		place to address the risk of discrepant monitoring of plasma levels and the measures to avoid this as applicable.'	
Section 8 Risk Management plan (line 472 to 527)	4	Comment: This section needs to be updated to reflect requirements of new benefit-risk management template. In particular advice would be welcome about how to assess real-life effectiveness as would any study designs and registries that might be utilised.	Not accepted. This goes beyond the scope of this rapid revision. Note: an EMA workshop on haemophilia registries will take place in July 2015.