European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 23 July 2009
Doc. Ref. EMEA/CHMP/BPWP/144552/2009

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

GUIDELINE ON THE CLINICAL INVESTIGATION OF RECOMBINANT AND HUMAN PLASMA-DERIVED FACTOR IX PRODUCTS

DRAFT AGREED BY BLOOD PRODUCTS WORKING PARTY	June 2009
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	23 July 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 October 2009
AGREED BY BPWP	
ADOPTION BY CHMP	
DATE FOR COMING INTO EFFECT	

This guideline replaces Guideline on the clinical investigation of recombinant factor VIII and IX products (CPMP/BPWG/1561/99) and Guideline on the clinical investigation of human plasma-derived factor VIII and IX products (CPMP/BPWG/198/95).

IMPORTANT NOTE

Draft revisions of CPMP/BPWG/1561/99 and CPMP/BPWG/198/95 were released for public consultation in July 2007. Following this consultation, it has been decided to reorganise the guidance to have separate guidelines for factor VIII and factor IX. The purpose of this second public consultation is to specifically seek comments on aspects of the guideline where there are significant changes in the recommendations from the previous draft revision as a result of comments received, namely:

- Children under 12 years
- PUPs
- Risk management plan
- Changes in the manufacturing process

Please do not provide comments on other parts of the guideline that were already provided during the 2007 consultation. These are being taken into account in this on-going revision process and an overview of all comments received with outcomes will be published at the time of finalisation of the guideline.

The Core SmPC will be amended accordingly.

Comments should be provided using this template to ludmila.svobodova@emea.europa.eu

KEYWORDS	*Recombinant factor IX, plasma-derived factor IX, efficacy, safety, immunogenicity, inhibitor, thrombogenicity, anaphylactic reactions*

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GLOSSARY

BU - Bethesda Unit
ED - Exposure Day
PTP - Previously Treated Patient
PUP - Previously Untreated Patient

EXECUTIVE SUMMARY

This guideline describes the information to be documented when an application for a marketing authorisation for recombinant or plasma-derived factor IX products is made for use in treatment and prevention of bleeding in patients with haemophilia B. The guideline covers clinical investigations to be conducted pre- and post-marketing authorisation. The guideline is also provided for authorised products where a significant change in the manufacturing process has been made.

1. INTRODUCTION

The purpose of this guideline is to provide applicants and regulators with harmonised requirements for applications for marketing authorisation for recombinant or plasma-derived factor IX products.

Before 1960 plasma was the only agent generally available for the treatment of hereditary coagulation disorders. Several plasma product concentrates are now available for this purpose, which have been purified and virally inactivated using various principles. In factor IX deficiency, replacement therapy consists of factor IX products of different purity. The recognition in the mid-1980's that coagulation factor concentrates had caused widespread transmission of human immunodeficiency virus (HIV) and non-A non-B hepatitis (now recognised as mainly hepatitis C) resulted in major changes to manufacturing processes in order to introduce steps to inactivate or remove these and other blood-borne viruses. However, occasional incidents of transmission of blood borne viruses still occurred in the early 1990's. It is, therefore, essential to ensure the safety of plasma-derived products by minimising contamination of the starting plasma and maximising the elimination of pathogens during production. In view of outbreaks of hepatitis A among haemophiliacs treated with a solvent detergent factor VIII in 1992 and later, the Committee on Proprietary Medicinal Products (CPMP) approved the position paper of the Biotechnology Working Party (III/5830/93) on blood products and non-enveloped viruses, recommending that the manufacturing process should include a viral inactivation/removal step which is also effective against non-enveloped viruses. This recommendation was further developed by revision of the CPMP notes for guidance on viral validation, and on plasma-derived products. Changes in the manufacturing procedures may lead to significant changes in the product, and may thereby alter the structure of the coagulation factor and its activity.

In view of the high rate of transmission of blood-borne viruses by plasma-derived (pd) coagulation factor concentrates in the 1970s and early 1980s, there was considerable interest on availability of factor IX products produced by recombinant DNA technology.

A comparison of pharmacokinetic parameters of recombinant factor IX and plasma-derived factor IX indicated that the elimination half-lives were nearly identical whereas the *in vivo* recoveries were statistically different. Differences in sulphation and lack of phosphorylation in recombinant factor IX may account for the lower recovery of recombinant factor IX as compared to plasma-derived factor IX.

Clinical trial data, addressing efficacy and safety with respect to immunogenicity and other adverse events, are required in patients of all age groups (patients >12 years and children aged 6-12 years and < 6 years) for an application for a marketing authorisation. Depending on the type of factor IX product (e.g. recombinant, novel modifications of manufacturing process) studies in previously untreated patients (PUPs) should be performed to investigate efficacy and safety in this specific patient population. In addition, the potential for thrombogenicity should be investigated in the case of factor IX products.

This guideline describes the clinical trials required for authorisation with respect to human plasma-derived and recombinant factor IX products.

These data are required for:

- products for which an application for a marketing authorisation is to be submitted, referred to as 'new products' in the text; and
- authorised products where a significant change in the manufacturing process has been made (e.g. additional viral inactivation/removal steps or new purification procedures).

The clinical trials described in this guideline should be performed according to the ICH E6 Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95).

According to best practice all haemophilia patients should be vaccinated against hepatitis A and B.

If a specific benefit of a certain product should be claimed e.g. a prolonged half-life which might lead to modifications of the clinical trial, it is recommended that advice on the design of clinical studies is sought via a European scientific advice procedure.

2. SCOPE

The guideline covers clinical investigations to be conducted pre- and post-marketing authorisation. Quality aspects are outside the scope of this guideline.

3. LEGAL BASIS

This guideline has to be read in conjunction with the introduction and general principles (4) and part I of the Annex I to Directive 2001/83 as amended.

4. EFFICACY

When clinically evaluating human plasma-derived or recombinant coagulation factors for the treatment of haemophilia B patients, the initial trial typically examines the pharmacokinetics of the principal active factor. Appropriate pharmacokinetic data (incremental recovery, half-life, area under the curve (AUC), and clearance) are the most important (surrogate) endpoints for efficacy of a new factor IX product. The International Society on Thrombosis and Haemostasis (ISTH)[1] also provides guidance on pharmacokinetic studies. It could be useful to consult this guidance for advice when designing studies.

5. SAFETY

Safety aspects of factor IX products include viral safety, immunogenicity and other adverse events. For recombinant products the use of non-human cell-lines raises the possibility of different contaminants and altered immunogenic potential. Thrombogenicity should also be considered a safety issue.

5.1 Adverse events

All adverse events occurring in relationship with any use of the product should be recorded and reported to competent authority.

Depending on the type of product the development of hypersensitivity reactions to heterologous proteins (e.g. murine, bovine or hamster origin) with related adverse reactions should be recorded and reported.

5.2 Safety with respect to viruses and other transmissible agents

Recombinant products

The safety of recombinant products with regard to viral contamination can only be reasonably assured by the application of virus testing within the manufacturing process and assessment of virus inactivation and removal during the manufacturing process, according to the relevant guidelines (e.g. ICH Q5A 'Note for Guidance on quality of biotechnological products: viral safety evaluation of biotechnology products derived from cell lines of human or animal origin' (CPMP/ICH/295/95)).

Plasma-derived products

[1] http://www.isth.org/

Manufacturers of plasma-derived products, including factor IX products, are obliged to optimise viral safety by selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective steps for the inactivation/removal of viruses in manufacturing processes.

The above-mentioned procedures are now considered to be highly effective and demonstrative of the viral safety of the product with respect to enveloped viruses. Therefore it is no longer considered appropriate to use clinical trials to investigate viral safety with regard to enveloped viruses.

These procedures may be of limited value against non-enveloped viruses, such as hepatitis A virus and parvovirus B19. The safety of the products with respect to non-enveloped viruses cannot currently be adequately evaluated in clinical studies.

The applicant is nevertheless required to provide all available data gathered on patients treated with the product in clinical trials. Investigators should continue with their normal clinical practice of monitoring patients. The applicant should demonstrate that there are systems in place to collect information on patients treated with the product and to respond rapidly to any reports of infection with a full investigation.

For products with an entirely novel manufacturing process other principles may apply. These applications should be discussed with the Regulatory Authorities prior to submission.

Other transmissible agents

Similar principles to those outlined for viral safety should apply for all transmissible agents including TSE and other emerging pathogens. Manufacturers should follow the respective guidance documents and position statements. Information can be found in the section "Guidelines on Plasma-derived Medicinal Products" on the EMEA website:
(http://www.emea.europa.eu/htms/human/humanguidelines/biologicals.htm).

5.3 Immunogenicity

In general, immunogenicity should be investigated prior to marketing authorisation and substantiated with post-marketing studies.

Haemophilia B is around 4 times less common than haemophilia A. The incidence of inhibitors in these patients following administration of factor IX is less common compared to the incidence found in haemophilia A patients. Inhibitors to factor IX have been demonstrated in approximately 4% of patients with severe haemophilia B. It has been observed that the occurrence of inhibitors is commonly associated with the total deletion of the factor IX gene. However, with regard to investigation of development of antibodies, the basic principles as outlined for haemophilia A patients in chapter 5.3 of Guideline on the Clinical Investigation of Recombinant and Human Plasma-derived Factor VIII Products (EMEA/CHMP/BPWP/144533/2009) should be taken into account where applicable. Unlike those with haemophilia A, patients with haemophilia B more often experience anaphylactic reactions to factor IX products in association with the development of inhibitors. Literature also reports on the occurrence of anaphylactic type reactions as well as the development of a nephritic syndrome following immune tolerance therapy. These problems have been observed for plasma-derived as well as for recombinant factor IX products.

5.4 Thrombogenicity

Treatment with plasma-derived factor IX products that contain factors II, VII and X has been associated with thrombosis. Factor IX products with higher purity have displayed less risk of thrombogenicity. For new factor IX products, tests for markers of activation of coagulation should be carried out in pre- and post-infusion samples obtained in the non-bleeding state.

6. APPLICATION FOR MARKETING AUTHORISATION: "NEW PRODUCTS"

This chapter is about either recombinant or plasma-derived factor IX products for which a new marketing authorisation is applied for.

6.1 General aspects on clinical trials

The clinical development for factor IX products should follow a stepwise approach in order to have some experience in older patients before investigating younger children. Therefore, the initial age cohort to be investigated are previously treated patients (PTPs) >12 years of age. Subsequently, when PK and efficacy/safety in 10 PTPs evaluated for at least 50 EDs is completed, the clinical investigation in children <12 years should be initiated. The clinical trial in 20 children should be started with PK followed by investigation of efficacy and safety during at least 50 EDs. These data have to be provided within the initial application for marketing authorisation.

A PUP study needs to be conducted for all new recombinant factor IX products and for factor IX products manufactured with novel production methods. PUPs are excluded from the indication until data from 20 PUPs investigated for efficacy and safety for at least 50 EDs are available. In case of plasma-derived factor IX products (e.g. manufactured with known methods) the need for PUP studies will be considered on a case by case basis. Applicants will receive feedback on this issue when submitting paediatric investigation plans or waivers and may also seek scientific advice to clarify this issue.

In view of the limited number of patients in the pre-authorisation trials, further information mainly focussing on safety aspects is needed to be achieved by post-marketing investigations. Please refer to Annex I "Overview on Clinical Trial Concept" and Annex II "Clinical Trials for Factor IX Products "New Products".

6.2 Efficacy

A pharmacokinetic trial, should be performed in at least 13 PTPs (>150 exposure days (EDs)) suffering from haemophilia B (factor IX ≤2%). The study should record incremental recovery, *in vivo* half-life, area under the curve (AUC), and clearance in patients without inhibitors who are not actively bleeding. Patients should be at least 12 years of age and should not have received an infusion of any factor IX product for at least 4 days. Prior to the first administration of the factor IX product, half life of the previous product should be investigated in all patients. Samples should be taken before injection of 50-75 IU/kg of the factor IX product and at 30 minutes, 1-3, 4-6, 7-9, 10-14, 20-26, 28-30 and 32-48 hours after the infusion. Depending on the type of factor IX product (e.g. prolonged half-life) further sampling time points could be necessary. At least 3 different lots should be employed in the trial. Incremental recovery is determined as the peak level recorded 30 minutes after infusion and reported as [IU/ml]/[IU/kg]. As several methods are possible, the assay used should be described. Preferably the same assay should be used for analysis of the product and the patient's plasma.

It is very important to record the exact time post-infusion at which the actual samples were collected and to use these precise values in the analysis.

Patients taking part in the pharmacokinetic trial should continue treatment with the product for 6 months, and should be re-tested for the same pharmacokinetic parameters after 3-6 months using the same dose as in the first investigation. Inhibitor testing should also be performed.

Clinical efficacy of factor IX should be evaluated in at least 20 PTPs (>12 years, >150 EDs), suffering from severe haemophilia B (factor IX ≤ 2%) and immunocompetent (CD4 > 200/μL). During an observation period of a minimum of 50 exposure days, clinical response should be assessed by the patients. Response should be assessed as "none", "moderate", "good" or "excellent" by the physician for those patients who were treated in hospital with the product for major bleeds. In addition, response will be determined by the physician in a minimum of 5 patients undergoing at least 10 surgical procedures (comprising major surgeries), including efficacy of haemostasis, loss of blood, and requirements for transfusion.

For the assessment of clinical efficacy of factor IX claimed in long-term prophylaxis, patients should be followed for 6 months for bleeding episodes, bleeding intervals and number of treatments.

Clinical efficacy should be assessed by calculating the consumption of factor IX, expressed as number of infusions and IU/kg per month and per year, as well as IU/kg per event (prophylaxis, on-demand, and surgery).

Continuous infusion

If a claim for continuous infusion treatment is requested, clinical data are required to establish the efficacy and safety. A suggested protocol is described below.

The study should be carried out in at least 10 severe haemophilia B (FIX ≤2%) patients undergoing elective major surgical procedures.

Prior to surgery, a pharmacokinetic analysis in each individual should be performed to obtain, in particular, an estimate of clearance. The initial infusion rate could be based on the clearance as follows:

Clearance x desired steady state level = infusion rate (u/kg/hr)

(if necessary plus a corresponding safety margin)

After the initial 24 hours of continuous infusion, the clearance should be calculated again every day using the steady state equation with the measured level and the known rate of infusion.

Efficacy and safety data during surgery and for at least 6 days thereafter should be submitted, including PK parameters with the description of the assay used, daily dosage of factor IX with the description of the administration method used, administration rate, haemostatic response and blood loss, transfusion requirements and local and systemic adverse effects.

Pharmaceutical data on reconstitution and stability of the product should be provided in the Quality section of the dossier.

6.3 Safety

Safety including vital parameters will be assessed in all patients receiving the factor IX product during clinical trials. All adverse events in clinical studies must be recorded and analysed with regard to causality, seriousness and expectedness. A detailed protocol of the studies specifying the methods for collection, intervals for collection of the data and duration of follow up is requested. In addition, appropriate tests for activation of coagulation (prothrombin fragment 1+2, thrombin-antithrombin (TAT) and D-dimer) should be carried out after administration of the product. This should be determined in the patients participating in the pharmacokinetic trial. Clinical evaluation of thrombosis should be undertaken by safe, objective means in a minimum of 5 patients undergoing at least 10 surgical procedures.

In patients developing anaphylaxis and/or inhibitors to factor IX, data on relevant antibodies, e.g. IgE, IgG, against factor IX (using appropriate methods) should be submitted.

6.4 Clinical investigation in PTPs

Choice of patients

Previously treated patients (PTPs) with at least 150 treatment EDs to previous products are considered as low risk patients and should be evaluated for product related immunogenicity. These PTPs should be above 12 years of age, with a factor IX level ≤2% and immunocompetent (CD4 lymphocytes >200/µl). The viral status of patients should be documented (HIV negative or a viral load < 200 particles/µl ~ <400000 copies/ml).

Due to the lower incidence of haemophilia B as compared to haemophilia A, at least 20 frequently treated patients should be followed and documented for a minimum of 50 exposure days. These data should be provided with the application. Where patients are only rarely treated during a 6-month period (i.e. less than 10 total exposure days) they will not count towards the total number studied for immunogenicity, but should be included for other parameters of safety.

Immunogenicity testing

The factor IX inhibitor titre should be determined by following the schedule set out in Annex IV. In the clinical studies, it is proposed to perform sampling for inhibitor measurements not less than 3 days after the previous administration, if possible. For all patients who develop inhibitors a full clinical report should be provided including clinical relevance, the cumulative incidence and the number of exposure days. The titre of the inhibitor should be reported in Bethesda Units (BU) using the Bethesda

assay. Plasma samples of patients who are suspected of inhibitors or who have developed inhibitors should be stored for possible future testing. These samples should be stored at least until evaluation of the clinical study by the competent authority. For further details please refer to chapter 5.3 of Guideline on the Clinical Investigation of Recombinant and Human Plasma-derived Factor VIII Products (EMEA/CHMP/BPWP/144533/2009).

Viral safety

Compliance with CHMP recommendations with regard to viral safety (see chapter 5.2) is necessary for all plasma-derived products and is verified by information supplied in Module 3 of the dossier.

A pre-treatment serum sample from each patient included in the clinical trials should be stored at -70˚C for possible future testing.

6.5 Clinical investigation in PUPs

Previously untreated patients (PUPs) are defined as those patients who have never been treated with clotting factor products (except previous exposure to blood components). Clinical trials in PUPs are required depending on the type of factor IX product (e.g. recombinant, novel methods of manufacturing process). For plasma-derived factor IX products the need to perform PUP studies will be considered on a case by case basis.

PUPs are excluded from the indication until data from 20 PUPs investigated for efficacy and safety are available. The approval of the indication in PUPs will be based on a clinical trial in a minimum of 20 PUPs evaluated for efficacy and safety during at least 50 ED connected with a post-authorisation commitment to follow-up at least 40 PUPs for a minimum of 100 ED.

The clinical trial in PUPs should be started when data from 10 patients participating in the children trial (0-12 years) from 50 ED are available, including data from a minimum of 5 patients <6 years, and pharmacokinetic investigations in children (0-12 years) are completed.

6.6 Clinical investigation in children

Since children may respond differently compared to adults, an open multicentre trial in children should be conducted. Due to the lower incidence of haemophilia B as compared to haemophilia A, the number of previously treated patients to be enrolled should be at least 20 children allocated to 2 age cohorts. A minimum of 10 patients should be PTPs at the age of 6-12 years and at least 10 patients should be <6 years who have undergone >50 EDs with previous factor IX products. The clinical trial in children should not start before data are available on 50 EDs for 10 patients (>12 years) who are included in the PTP trial.

The clinical trial in children should begin with the investigation of pharmacokinetics (incremental recovery, *in vivo* half-life, AUC and clearance) in 10 patients of each age cohort. In order to allow for a comparison, existing PK data with the previous product could be submitted. However, there should be a recent investigation of the half-life of the previous product prior to start with treatment with the investigational medicinal product. With regard to patient compliance, PK sampling time points can be reduced to measurements prior to infusion (baseline) and 30min, 1-3, 4-6, 10-14, 20-26 32-48 hours after infusion. Depending on the type of factor IX product (e.g. prolonged half-life) further sampling time points could be necessary. It is anticipated that some deviation from the recommendation may occur in clinical practice, therefore, it is very important to record the exact time post-infusion at which the actual samples were collected and to use these precise values in the analysis.

Preferably, the testing should be conducted in a central laboratory to decrease variability in test results. Factor IX consumption (dose/kg for prophylaxis and therapy (on demand)) should be monitored as well as development of inhibitors in all the children participating in the study. Inhibitor testing should be performed following the same testing schedule as set out in Annex IV or if there is any suspicion of inhibitor (see also chapter 5.3 of Guideline on the Clinical Investigation of Recombinant and Human Plasma-derived Factor VIII Products (EMEA/CHMP/BPWP/144533/2009)). In accordance with the requirements for the pre-authorisation PTP trial, the study in children should continue until the patients have received a minimum of 50 EDs to the investigational product. For all patients who develop inhibitors, a full clinical report should be provided including clinical relevance, the

cumulative incidence and the number of EDs in relation to development of inhibitors. The titre of the inhibitor should be reported in Bethesda Units. Plasma samples from patients who are suspected of inhibitors should be stored for possible future testing.

Within the application for marketing authorisation, pharmacokinetic data (incremental recovery, *in vivo* half-life, AUC and clearance) as well as the completed efficacy and safety trial in 20 children (0-12y) followed for 50 EDs should be submitted.

For the post-marketing investigation, PTPs (>150 EDs) regardless of their age can be included provided that the study in children is finished.

The requirements of the paediatric regulation (EC) No 1901/2006, as amended, should be taken into account.

6.7 Post-marketing investigation

In view of the limited number of patients, data from pre-licensing studies are insufficient to estimate all aspects of therapy with factor IX. Therefore, to collect additional clinical data and to ensure consistency in the long-term between the outcome from the clinical studies and from routine use, a post-marketing investigation has to be performed. The clinical study protocol should be submitted with the application for marketing authorisation as part of the risk management plan (see Guideline on Risk Management Systems for Medicinal Products for Human Use (EMEA/CHMP/96268/2005)). The results of the PTP study should be taken into account for the design of the post-marketing study. Besides aspects like clinical efficacy and general product safety, there has to be a focus on immunogenicity, particularly on inhibitor development, anaphylactic reactions and thrombogenic effects. The general principles of immunogenicity and inhibitor documentation as laid down in chapter 5.3 of Guideline on the Clinical Investigation of Recombinant and Human Plasma-derived Factor VIII Products (EMEA/CHMP/BPWP/144533/2009) should be taken into account.

The study should reflect the population in the countries where the product is intended to be marketed. A detailed patient documentation (diary, logbook etc.) covering the last 50 exposure days/per patient or the last 2 years of therapy to confirm treatment modality (i.e. prophylaxis, on demand or recent surgery) is needed and should be available upon request. Patients with severe haemophilia after successful Immune Tolerance Induction (ITI) can be included, in order to obtain valuable information in this patient cohort. The proportion of these ITI patients should not be more than 25% of the whole cohort.

The minimum number of patients to be enrolled in a post-marketing investigation with factor IX product is 50. In case of plasma-derived factor IX products (e.g. manufactured by known methods, for national approval only) a smaller number of patients could be enrolled but justification should be provided.

Study participants should be PTPs (>150EDs), and could be recruited regardless of their age, however, aiming for a balanced age distribution.

The post-marketing investigation protocol will be approved at marketing authorisation as a part of the risk management plan. A separate progress study report should be provided to competent authorities 2 years after marketing authorisation. The post-marketing investigation should be completed within 4 years.

For detailed requirements of study design please refer to Annex IV.

7. CHANGE IN MANUFACTURING PROCESS

Changes in the manufacturing process may lead to significant changes in the product and may thereby alter the structure of the coagulation factor and its activity. The effects of changes in the manufacturing process (e.g. viral inactivation steps or purification procedures) on the biological characteristics and activity of the product should be investigated. If significant impact on the activity of the coagulation factor cannot be excluded, data on pharmacokinetics, efficacy and safety should also be provided with the application. These data should be generated by following the comparability exercise (see ICH Q5E Note for Guidance on Biotechnological/Biological Products Subject to Changes in their Manufacturing Process (CPMP/ICH/5721/03) and Guideline on comparability of

biotechnology-derived medicinal products after a change in the manufacturing process non-clinical and clinical issues (EMEA/CHMP/BMWP/101695/2006).

7.1 General aspects on clinical trials

When a change is introduced to the manufacturing process of a given product, the marketing authorisation holder will have to demonstrate that the "post-change" and the "pre-change" product are comparable in terms of quality, safety and efficacy (see Guidelines on Comparability). This might be a sequential process, beginning with investigations of quality and supported, as necessary, by non-clinical and/or clinical studies.

The extent of clinical data to be provided has to be judged on a case by case basis depending on the anticipated impact of the changes and could vary from pharmacokinetic investigations comparing "pre-change" versus "post-change" product up to the full clinical data set as outlined for a new product (see chapter 6).

Of special interest will be whether the immunogenicity profile of the "post-change" product remains the same when compared to the "pre-change" product. Depending on the anticipated risk, a study monitoring the switch between "pre-change" and "post-change" product could be required.

As a consequence, applications should be accompanied by assessment of the potential impact of a change on efficacy and safety of a given product and the rationale behind the clinical development plan should be outlined and justified.

7.2 Efficacy

Evidence should be provided to demonstrate that the change in the manufacturing process has not affected the pharmacokinetics of the product. Guidance is provided in the Guideline on comparability of biotechnology-derived medicinal products after a change in the manufacturing process non-clinical and clinical issues (EMEA/CHMP/BMWP/101695/2006), Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004) and Note for Guidance on the Investigation of Bioavailability and Bioequivalence (EMEA/EWP/QWP/1401/98).

A comparative pharmacokinetic trial with the "pre-change" product versus the "post-change" product should be performed in at least 13 PTPs suffering from haemophilia B (factor IX ≤2%). The study should record incremental recovery, *in-vivo* half-life, area under the curve (AUC), and clearance in patients without inhibitors who are not actively bleeding. Patients should be at least 12 years of age and should not have received an infusion of any factor IX product for at least 4 days. Samples should be taken before injection of 50-75 IU/kg of the factor IX product and at 30 minutes, 1-3, 4-6, 7-9, 10-14, 20-26, 28-30 and 32-48 hours after the infusion. Depending on the type of factor IX product (e.g. prolonged half-life) further sampling time points could be necessary. At least 3 different lots of "post-change" product should be employed in the trial. Incremental recovery is determined as the peak level recorded 30 minutes after infusion and reported as [IU/ml]/[IU/kg].

It is very important to record the exact time post-infusion at which the actual samples were collected and to use these precise values in the analysis.

Patients in the pharmacokinetic trial should continue treatment with the "post-change" product for 6 months, and should be re-tested for the same pharmacokinetic parameters after 3-6 months using the same dose as in the first investigation.

Should any of the patients participating in the clinical trials undergo surgical procedures, response will be determined by the physician, including efficacy of haemostasis, loss of blood, requirement for transfusion and occurrence of thromboembolic episodes.

7.3 Safety

Please refer to the requirements for new factor IX products in chapter 6.3.

Clinical evaluation of suspected incidences of thrombosis should be undertaken by safe, objective means in any patients undergoing surgical procedures.

7.4 Clinical investigation in PTPs

Please refer to the requirements for new factor IX products in chapter 6.4.

7.5 Clinical investigation in PUPs

Please refer to the requirements for new factor IX products in chapter 6.5.

7.6 Clinical investigation in children

Please refer to the requirements for new factor IX products in chapter 6.6.

7.7 Post-marketing study

Please refer to the requirements for new factor IX products in chapter 6.7.

8. RISK MANAGEMENT PLAN

The following points should be considered in the relevant sections of the Risk Management Plan (RMP) for new factor IX products as well as for factor IX products with a significant change in the manufacturing process. For factor IX products with a significant change in the manufacturing process, extrapolation of safety data from previous product needs to be fully justified.

Risk Management Plans should be compiled in compliance with the provisions of the Guideline on Risk Management Systems for Medicinal Products for Human Use (EMEA/CHMP/96268/2005). The protocol of the post-marketing investigation should be included in Annex 5 of the RMP.

Identified/ potential risks

- Inhibitor formation

The most serious complication in haemophilia is the development of inhibitors in PUPs and PTPs although inhibitor occurrence in haemophilia B is less common than in haemophilia A. A comprehensive analysis of reported *de novo* and recurrent inhibitors should be provided. Inhibitors should be discriminated concerning:

- Source of inhibitor reports (e.g. Clinical Trial/post-authorisation investigation/spontaneous reports)
- Low and high titre, intermittent inhibitor. (Every positive laboratory test should be retested in a central laboratory with a second separately drawn sample from the same patient before a diagnosis of an inhibitor can be made. Samples should be stored for possible future testing.)
- Class 1 and 2 inhibitors
- Classification of risk to develop factor IX inhibitor.
  - Haemophilia severity
  - Status of treatment (i.e. PUP/PTP)
  - Cumulative exposure to factor IX containing products (total ED and ED on product)
- Known risk factors that have impact on the development of inhibitors are e.g.:
  - Type of gene mutation
  - Ethnicity
  - Age at first treatment
  - Intensity of treatment
  - Severity of haemophilia

Inhibitor frequency should be expressed as point estimate and 95 % CI.

- Lack of Drug effect

Lack of drug effect and breakthrough bleeding may point to inhibitor development. A pre-defined case definition is essential. Careful follow up including inhibitor evaluation (consumption, recovery, half-life, inhibitor testing) needs to be documented.

- Hypersensitivity/anaphylactic reactions

Hypersensitivity/anaphylactic reactions, including against host cell proteins used in the manufacturing process, may occur. These reactions should be classified according to skin associated and systemic hypersensitivity reactions. Patients developing anaphylaxis should be carefully investigated and followed-up for inhibitor development. An appropriate questionnaire should be used with information collected on status of treatment (e.g. PUP/PTP). Data on relevant antibodies, e.g. IgE, IgG, against factor IX (using appropriate methods) should be submitted.

- Thrombogenicity

Missing information

If applicable the following information should be provided:

- Inhibitor formation in PUPs
- Specific paediatric age group(s)
- Patients with history of inhibitor to another medicinal product and the risk for recurrent inhibitors
- Immune tolerance induction

Efforts should be made to provide guidance about the correct dose for ITI in patient with inhibitors to factor IX, and to identify predictors of immune tolerance success.

- Special populations:
  - Patients who underwent surgery and subsequently develop inhibitors
  - Any specific risk (e.g. inhibitor development, lack of effect) induced in switching to the product from another factor IX should be discussed separately. This is in particular relevant for products with a significant change in the manufacturing process. The switch from "pre-change" to "post-change" product should be investigated carefully.

REFERENCES

Guidelines on:

Guideline on the Clinical Investigation of Recombinant and Human Plasma-derived Factor VIII Products (EMEA/CHMP/BPWP/144533/2009)

Clinical Trials

ICH E6 Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)

First use in Man

Guideline on strategies to identify and mitigate risks for first-in human clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07)

Small populations

Guideline on clinical trials in small populations **(**CHMP/EWP/83561/2005)

Comparability

ICH Q5E Note for Guidance on Biotechnological/Biological Products Subject to Changes in their Manufacturing Process (CPMP/ICH/5721/03)

Guideline on comparability of biotechnology-derived medicinal products after a change in the manufacturing process non-clinical and clinical issues (EMEA/CHMP/BMWP/101695/2006)

Further guidance on pharmacokinetic comparability

Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004)

Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98)

Risk management plan

Guideline on risk management systems for medicinal products for human use (EMEA/CHMP/96268/2005)

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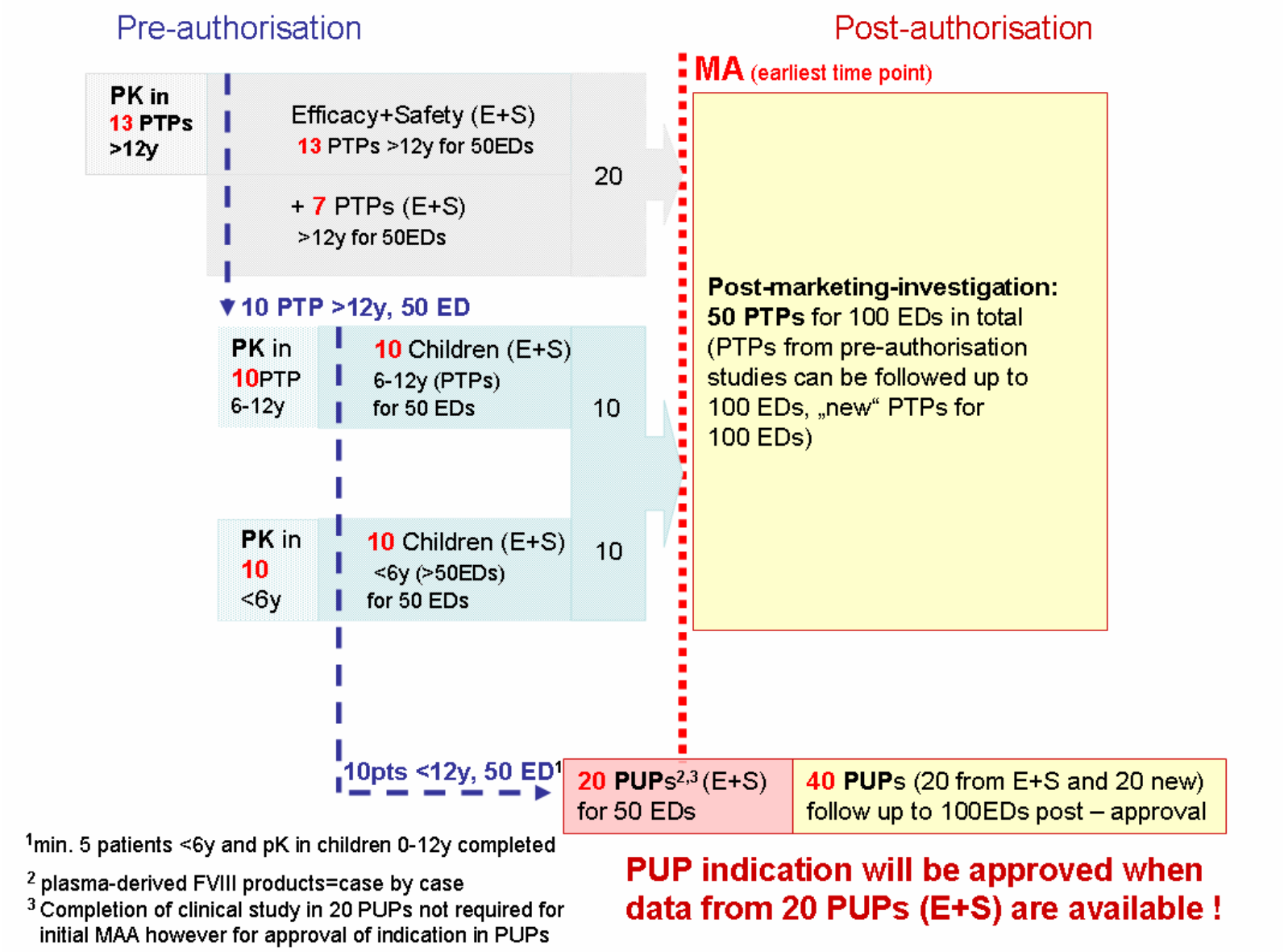

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ANNEX II – CLINICAL TRIALS WITH FIX PRODUCTS: NEW PRODUCTS

TRIAL, SUBJECTS	INVESTIGATION	PARAMETERS
PTP Study Pre-authorisation		
13 haemophilia B patients (factor IX ≤2%) without inhibitors and not actively bleeding	Pharmacokinetics	Incremental recovery, half-life*, AUC, clearance.
		Patients should be re-tested after 3-6 months (including factor IX inhibitor assay).
	Safety	Blood pressure, heart rate, temperature, respiratory rate and adverse events. Thrombogenicity.
5 haemophilia B patients undergoing at least 10 surgical procedures	Clinical efficacy	Efficacy of haemostasis, loss of blood and requirement for transfusion. Factor IX consumption.
	Safety	Adverse events. Thrombogenicity.
Efficacy and Safety in 20 PTPs (>12 years; factor IX ≤2% and CD4>200/µl)	Clinical efficacy	Factor IX consumption, physician's assessment of response in treatment of major bleeds.
	Immunogenicity	Inhibitor titre in Bethesda Units immediately before first exposure, ED1, ED10-15, ED50-75 and if there is any suspicion of inhibitor development, continue for a minimum of 50 exposure days.
	Safety	Adverse events. Thrombogenicity.
Children Study – Pre-authorisation (to be started after results of 50 ED in 10 PTPs (>12 years) have become available).		
10 haemophilia B patients (PTPs,**6-12y**; factor IX ≤2%) without inhibitors and not actively bleeding 10 haemophilia B patients (<50EDs, **<6y**, factor IX ≤2%) without inhibitors and not actively bleeding	Pharmacokinetics Safety	Incremental recovery, half-life*, AUC, clearance. Blood pressure, heart rate, temperature, respiratory rate and adverse events. Thrombogenicity.
Open multicentre trial in 20 children with haemophilia B allocated to 2 age cohorts: 10PTPs (6-12 years); 10 children (<6 years; >50EDs).	Clinical efficacy	Factor IX consumption, physician's assessment of response in treatment of major bleeds.
	Immunogenicity	Inhibitor titre in Bethesda Units immediately before first exposure, ED1, ED10-15, ED50-75 and if there is any suspicion of inhibitor development. Follow-up for a minimum of 50 exposure days.
	Safety	Adverse events. Thrombogenicity.
Post-marketing investigation		
50 PTPs for 100 EDs in total (PTPs from pre-authorisation studies can be followed up to 100 EDs, "new" PTPs for 100 EDs)	Clinical efficacy Immunogenicity Safety	Protocol should be provided according to Annex IV.
PUP Study (to be started after results of 50 ED in 10 children (0-12y, at least 5 of them <6y) are available and PK in children 0-12y completed.)		
20 PUPs for at least 50 EDs	Clinical efficacy	Factor IX consumption, physician's assessment of response in treatment of major bleeds.
	Immunogenicity	Inhibitor testing immediately before first exposure, ED1, ED10-15, ED50 or if there is any suspicion of inhibitor development. Continue until a minimum of 50 exposure days.
	Safety	Adverse events
Post approval-commitment of PUP indication 40 PUPs should be followed up to 100 EDs (20 PUPs from pre-approval PUP indication can be followed up to 100 EDs, 20 "new".PUPs for 100 EDs).		

*half-life should also be measured with the previous product.

ANNEX III – CLINICAL TRIALS WITH FIX PRODUCTS FOLLOWING CHANGES[2]

TRIAL, SUBJECTS	INVESTIGATION	PARAMETERS
13 haemophilia B patients (PTPs; factor IX ≤2%) without inhibitors and not actively bleeding	Pharmacokinetics	Comparative trial pre-change vs. post-change product: incremental recovery, half-life, AUC, clearance. Patients should be tested again after 3-6 months.
	Safety	Blood pressure, heart rate, temperature, respiratory rate and adverse events. Thombogenicity.
Any haemophilia B patients undergoing surgical procedures	Clinical efficacy	Efficacy of haemostasis, loss of blood and requirement for transfusion. Factor IX consumption.
	Safety	Adverse events. Thrombogenicity.
PTP study 20 PTPs (>12 years; factor IX ≤2% and CD4>200/µl) Children and PUPs if applicable (see Annex II)	Clinical efficacy	Factor IX consumption, physician's assessment of response in treatment of major bleeds.
	Immunogenicity	Inhibitor titre in Bethesda Units immediately before first exposure, ED1, ED10-15, ED50-75 and if there is any suspicion of inhibitor development. Follow-up for a minimum of 50 exposure days.
	Safety	Adverse events. Thrombogenicity
Post-marketing study	Clinical efficacy Immunogenicity Safety	Protocol should be provided.
Pharmacovigilance "Switch Study"	Monitoring switch from "pre-change" to "post-change" product	Protocol should be provided if applicable

[2] "The extent of clinical data supporting a change of the manufacturing process for a factor VIII product could vary from a pharmacokinetic trial comparing pre-change versus post-change product up to the full clinical data set as outlined for a new product (see chapter 6)."

ANNEX IV – REQUIREMENTS FOR POST-MARKETING INVESTIGATION

Inclusion criteria

- Diagnosis: haemophilia B
- Severity: ≤2% factor IX:C
- Number of exposure days before inclusion: >150 ED
- PTPs of every age group could be included, provided that trial in children is completed (PK and efficacy and safety) and report is submitted and evaluated by Competent Authority

Documentation of Patient's characteristics

- Gene defect
- Ethnicity
- Family history of haemophilia
- History of inhibitors
- Viral status (HIV should be negative or have a viral load <200 particles/µl ~ 400000 copies/ml)
- Co-morbidity or co-medication which would significantly impact blood coagulation or immunoreaction (any information concerning this issue should be included)

Patient enrolment

- At least 50 patients per post-marketing investigation study*
- Follow-up of each patient must be at least 100 ED

*Progress on recruitment has to be reported on a regular basis (will be set out before approval of procedure)

General performance

- Before patient inclusion there should not be a clinical suspicion of inhibitors and a recovery and inhibitor test in a central laboratory should confirm that the patient is inhibitor negative at study entry. An inhibitor test which is not negative should be confirmed by testing a second separately drawn sample in a central laboratory.
- Testing schedule (ED = Exposure Day)

	Previous product * #	Test product ED1*	Test product ED10-15*	Test product ED50-75*	Test product ED~100*
Inhibitor	x	x	x	x	x
Recovery	x	x	x	x	x

*after washout period (see Explanatory Note); storage of back up blood sample is recommended
#new patients = not recruited for pre-authorisation studies

Testing should also be carried out if there is any suspicion of an inhibitor.

- Patients' diaries should be evaluated on total number of exposures per year and mean dose per kg per patient/year (consumption).
- Intended treatment regimen for every patient at study entry and reason for each ED should be documented
- In case of bleeding: documentation of particulars; judgement of severity and treatment outcome by clinician and patient (consumption)
- In case of surgery different data are to be collected (surgical protocol) (e.g. type of surgery (planned or emergency); documentation of complications; mode of administration, consumption)

- Monitoring of all adverse events.

Explanatory Note

Inhibitor tests should be performed when the plasma factor IX level has reached a pre-substitution nadir (documentation for the last infusion should be provided). In the case that patients are treated on demand, an inhibitor can be missed when the patients did not receive treatment for > 2 weeks. According to the t1/2 of immunoglobulins, the inhibitor will drop gradually when treatment has been stopped. In case of a positive inhibitor test, also PK/ recovery tests are necessary to confirm inhibitory activity.

Co-medication: At the present time, all patients are accepted in studies (provided they are immunocompetent CD4 lymphocytes >200/µl, HIV negative or having a viral load <200 particles/µl ~ 400000 copies/ml). Patients with HIV infection receive intensive co-medication and it is unknown whether this, e.g. HAART therapy, can influence inhibitor formation or efficacy of treatment. Similar problems can be expected for HCV positive patients, some receive therapy and others have lower platelets and decreased liver function and altered coagulation. These patients can be included in order to provide additional data on efficacy in this group, but more parameters on co-morbidity should be collected.