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Guideline on the clinical investigation of recombinant and human plasma-derived factor IX products

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This guideline replaces 'Guideline on clinical investigation of recombinant and human plasma-derived factor IX products' (EMA/CHMP/BPWP/144552/2009 Rev. 1, Corr. 1)

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LIST OF ABBREVIATIONS

AUC – Area under the Curve

BU - Bethesda Unit

CI – Confidence Interval

E - Efficacy

ED - Exposure Day

HAART - Highly active anti-retroviral therapy

IS - International Standard

ITI – Immune Tolerance Induction

IU – International Units

MA – Marketing Authorisation

MAA – Marketing Authorisation Application

p-d - plasma-derived

PhVWP - Pharmacovigilance Working Party

PK – Pharmacokinetics

PMI – Post Marketing Investigation

PTP - Previously Treated Patient (defined as >150 EDs)

PUP - Previously Untreated Patient

RMP - Risk Management Plan

S - Safety

SAE – Serious Adverse Event

TSE – Transmissible spongiform encephalopathy

SmPC – Summary of Product Characteristics

y - years

Executive summary

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

History of guideline: The original Note for Guidance on Clinical Investigation of Human Plasma Derived FVIII and FIX Products (CPMP/BPWG/198/95) came into operation on 14 February 1996. The first revision (CPMP/BPWG/198/95 Rev. 1) came into operation in April 2001. The original Note for Guidance on Clinical Investigation on Recombinant FVIII and FIX Products (CPMP/BPWG/1561/99) came into operation in April 2001. Draft revisions of CPMP/BPWG/1561/99 and CPMP/BPWG/198/95 were released for public consultation in July 2007. Following this consultation, it was decided to reorganise the guidelines into separate documents for factors FVIII and FIX products: The Guideline on clinical investigation of recombinant and plasma derived factor VIII products (EMA/CHMP/BPWP/144533/2009) and this Guideline on clinical investigation of recombinant and plasma derived factor IX products (EMA/CHMP/BPWP/144552/2009).

EMA/CHMP/BPWP/144552/2009 came into effect on 1 February 2012. Revision 1 was a rapid revision following an EMA/EDQM workshop on potency assays that took place in 2013. Subsequently in July 2015, an EMA workshop on registries in haemophilia led to the recommendation that the clinical trial concept requiring studies for previously untreated patients (PUP) for factor IX products needed to be reconsidered for the following reasons. The number of suitable patients especially PUPs to be enrolled in clinical trials is problematic. Hence, the conduct of sufficiently informative clinical trials in PUPs to estimate important characteristics of single products was considered difficult. Following a public consultation in 2017, a second workshop on haemophilia registries was held on 8 June 2018 which aimed at defining the requirements for practical implementation using existing registries to support post-authorisation observational studies of haemophilia medicines. The workshop discussed recommendations on important aspects such as appropriate governance of registries, patient consent, data collection, data quality and data sharing, and interoperability between different registries. Following these workshops, the obligation to perform clinical trials in PUPs for marketing authorisation purposes has been deleted. Furthermore, a core parameter set for registry data collection in haemophilia is introduced. The opportunity was also taken to implement other minor updates.

1. Introduction (background)

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.

Clinical trial data, addressing efficacy and safety with respect to immunogenicity, thrombogenicity and other adverse events in all age groups, are required in an application for a marketing authorisation.

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).

This guidance introduces general principles on efficacy and safety in chapters 4 and 5. Information on the clinical development concept is included in subsequent chapters regarding "new products" and significant changes of the manufacturing process. Detailed "at a glance" requirements for clinical trials for factor IX products are found in Annexes I to III.

If the product is associated with specific characteristics that would warrant a modification of the clinical trial approach proposed in this guidance (e.g. a prolonged half-life or subcutaneous dosing), seeking scientific advice is recommended.

2. Scope

The guideline covers clinical investigations to be conducted pre- and post-marketing authorisation for all plasma-derived and recombinant factor IX products. In general, 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 Annex I to Directive 2001/83/EC as amended, as well as the Paediatric Regulation (EC) 1901/2006 as amended.

4. Overall clinical development programme

4.1. General aspects

In view of the limited availability of patients suffering from haemophilia B to participate in clinical studies, data from pre-authorisation studies only are considered insufficient to estimate all aspects of therapy with factor IX products, especially with respect to immunogenicity. Therefore, to collect additional clinical data and to ensure consistency in the long-term between the outcome from pre-authorisation clinical studies and from routine use, a post-marketing investigation should be performed.

Due to the rarity of the disease, it is challenging to conduct sufficiently informative randomized controlled trials. Therefore, considering the strong biological rationale of the treatment, i.e. replacing the missing FIX by plasma-derived or recombinant FIX, and also the knowledge that prevention or treatment of bleeding events is in fact associated with FIX levels, single-arm trials are considered acceptable in this specific setting. Further details regarding pharmacokinetic, efficacy and safety data to be derived are provided in subsequent chapters of this guideline.

The number of patients typically needed to be enrolled into the pre-authorisation clinical trials is a minimum of 40. This number was selected by balancing the minimal clinical evidence needed to demonstrate efficacy and safety against the availability of patients suffering from this rare disease. This number of patients is expected to be adequate to provide relevant information on general safety aspects and to 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. However 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.

The clinical development for factor IX products should follow a stepwise approach in order to have some experience in adults and older children before investigating younger children. Therefore, the initial age cohort to be investigated is previously treated patients (PTPs) ≥12 years of age. Subsequently, when PK and efficacy/safety in 10 PTPs ≥12 years for at least 50 exposure days (EDs) are available, the clinical trial(s) in children 0 - <12 years can be initiated. The clinical study in children of 0 - <12 years should be started with PK followed by investigation of efficacy and safety for at least 50 EDs each in 20 children.

These data have to be provided within the initial application for marketing authorisation. The clinical investigation in children needs to be supported by an approved paediatric investigation plan.

Please refer to Annex I 'Overview on Clinical Trial Concept' and Annex II 'Clinical Trials for Factor IX Products New Products'.

4.1.1. Potency measurement

A number of different assays for factor IX potency measurement are available and for some products significantly different product potencies can be obtained with the different methods/assays, reagents and reference standards that are available. These method-related potency discrepancies can impact both the finished product potency labelling and also the clinical monitoring post-infusion. A working group of the International Society of Thrombosis and Haemostasis (ISTH) has published "Recommendations on the potency labelling of factor VIII and factor IX concentrates".[*] These recommendations include advice for the characterization of products with respect to potency assays, calibration of manufacturers' product reference, pharmacokinetic studies and testing of post-infusion samples. A joint EMA/EDQM workshop on this topic was held in 2013 (see reference list).

Thorough characterisation of new factor IX products, taking into account ISTH recommendations, in a variety of potency assays against the WHO IS (concentrate and plasma) is important. In the case where significant potency discrepancies are observed depending on the method/assay variables used, it should be demonstrated that the particular assay design chosen for potency labelling supports comparability (with the unitage applied) to an appropriate, non-modified licensed product based on comparisons of *in vitro* and *in vivo* functionality. Consequences for laboratory monitoring of product plasma levels should be addressed in the risk management plan (RMP) and appropriate information should be given to users of the product.

4.2. General aspects for 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 potential safety issue.

[*] Recommendations on the potency labelling of factor VIII and factor IX concentrates (Hubbard AR, Dodt J, Lee T, Mertens K, Seitz R, Srivastava A, Weinstein M, on behalf of the Factor VIII and Factor IX Subcommittee of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. 2013: 11:988-9. doi: 10.1111/jth.12167).

4.2.1. Adverse events

Safety, including vital signs, should be assessed in all patients receiving the factor IX product during clinical trials and registry-based studies. All adverse events in clinical studies must be recorded and analysed with regards to causality, seriousness and expectedness.

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

Depending on the type of product, the development of hypersensitivity reactions to heterologous proteins (e.g. murine, bovine or hamster origin) may occur with related adverse events which should be recorded and reported. All study protocols should include a hypersensitivity questionnaire/reporting form to collect all relevant data in this regard.

4.2.2. 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 implementation of virus inactivation and removal steps 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

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. Similar principles to those outlined for viral safety should apply for all transmissible agents including Transmissible spongiform encephalopathy (TSE) and other emerging pathogens. Manufacturers should follow the respective guidance documents and position statements. Information can be found in the biological guidelines on the EMA website in the section "Guidelines on Plasma-derived Medicinal Products".

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 regards 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 is a pharmacovigilance system in place to collect information on patients treated with the product and to respond rapidly to any reports of infection with a full investigation.

4.2.3. Immunogenicity

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

The incidence of inhibitors (neutralising antibodies) in haemophilia B patients following administration of factor IX is less common compared to the incidence found in haemophilia A patients. It has been observed that the occurrence of inhibitors is commonly associated with the total deletion of the factor IX gene. However, with regards to investigation of development of antibodies, the basic principles as outlined for haemophilia A patients in chapter 5.3 of the Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products (EMEA/CHMP/BPWP/144533/2009 rev. 2) should be taken into account where applicable. In particular, neutralising antibodies are the most important immunological concern and therefore the same aspects and basic principles reported in the Guideline for recombinant and human plasma-derived factor VIII products should also be considered for factor IX products. 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 nephrotic syndrome following immune tolerance therapy. These problems have been observed for plasma-derived as well as for recombinant factor IX products.

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.

4.2.4. 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, appropriate tests for markers of activation of coagulation (prothrombin fragment 1+2, thrombin-antithrombin (TAT) and D-dimer) should be carried out in pre- and post-infusion samples obtained in the non-bleeding state. 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. Additional information on other covariates influencing the risk such as obesity, age, etc. might be important.

4.3. Clinical investigation in PTPs ≥12 years

4.3.1. Choice of patients

Previously treated patients (PTPs) with at least 150 treatment EDs to previous products are considered as low risk patients regarding development of inhibitors and should be evaluated for product related immunogenicity, pharmacokinetic parameters, safety and efficacy. These PTPs should be ≥12 years of age, with a factor IX level ≤2% and immunocompetent (HIV positive patients should have CD4 lymphocytes >200/µl). The viral status of patients should be documented. The patients should be HIV negative or have a viral load < 200 particles/µl or <400000 copies/ml. Due to the lower incidence of haemophilia B as compared to haemophilia A, at least 20 previously treated patients should be followed and documented for a minimum of 50 EDs. These data should be provided with the application.

4.3.2. Pharmacokinetics

A pharmacokinetic trial should be performed in at least 12 PTPs (for details of patient inclusion criteria see previous paragraph "choice of patients"). The study should record incremental recovery, terminal half-life ($t_{1/2}$), 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 4-6 days. In order to allow for evaluation of a patient's individual response, existing pharmacokinetic information with the patient's previous factor IX product (historical or recent recovery and half-life) should be available prior to first administration of the new factor IX product. Samples should be taken before injection of 50-75 IU/kg of the factor IX product (baseline), between 10-15 minutes (times refer to the interval after the completion of the infusion), at 30 minutes, and at 1, 3, 6, 9, 24, 48, and 72 hours post-infusion. Depending on the type of factor IX product (e.g. prolonged half-life) sampling time points should be adjusted to cover the main parts of the activity time profile, i.e. subsequent to the 1 hour sample at least 6 samples should be analysed to capture up to 5 half-lives. 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. As several assay 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 (see also 6.1.1).

It is very important to record the exact time interval post-infusion at which the samples were actually collected and to use these precise values in the analysis. In accordance with the Clinical investigation in children < 12 years of age, the testing should be conducted in a central laboratory to decrease variability in test results.

An additional description of the pharmacokinetic data according to body weight (normal range, overweight and underweight) should be provided.

Inhibitor testing should also be performed (see Annex II for further details).

If a factor IX product should be marketed in different strengths leading to a broad range of factor IX concentrations after reconstitution, the pharmacokinetics of the lowest and highest concentration should be investigated unless otherwise justified.

4.3.3. Efficacy including surgery

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 > 200/µL) as set out in Annex II. 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. The definition of the response criteria needs to be specified in the study protocol. In addition, response should 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 in long-term prophylaxis, patients should be treated for 6 months and assessed for bleeding episodes, bleeding intervals and number of treatments.

Clinical efficacy should also 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). Data on minor and major surgeries should be reported separately.

4.3.4. Continuous infusion

If continuous infusion therapy is claimed, the study should be carried out in at least 10 haemophilia B patients (FIX ≤2%) 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 (IU/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, consumption, haemostatic response and blood loss, transfusion requirements and local and systemic adverse events.

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

4.3.5. Immunogenicity testing

The factor IX inhibitor titre should be determined by following the schedule set out in Annex III. In the clinical studies, it is proposed to perform sampling for inhibitor measurements not less than 3 days after the previous administration, if possible. Product specific properties e.g. extended half-life should be taken into account to avoid interference from residual factor IX product. 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 or the Nijmegen modification of the Bethesda assay. Plasma samples from patients who are suspected of inhibitors or who have developed inhibitors should be stored until evaluation of the clinical study by the competent authority is completed in order to permit additional inhibitor analysis if needed. For further details, please refer to chapter 5.3.

4.3.6. Viral safety

Compliance with CHMP recommendations with regards to viral safety (see chapter 5.2) is necessary 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.

4.4. Clinical investigation in children <12 years

4.4.1. Choice of patients

Since children may respond differently compared to adults, a multicentre trial in children should be conducted. Due to the lower incidence of haemophilia B as compared to haemophilia A, the number of children to be enrolled should be at least 20, allocated to 2 age cohorts, as set out in Annex II. A minimum of 10 patients should be PTPs (>150 ED) 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 <12 years should not start before safety is proven for 50 EDs each of 10 patients who are included in the PTP trial ≥12 years.

4.4.2. Pharmacokinetics

The clinical trial in children should include investigation of pharmacokinetics (incremental recovery, $t_{1/2}$, AUC and clearance) in 10 patients of each age cohort. In order to allow for evaluation of a patient's individual response, existing pharmacokinetic information with patient's previous factor IX product (historical or recent recovery and half-life) should be available prior to first administration of the new factor IX product. With regards to patient compliance, PK sampling time points can be limited to measurements prior to infusion (baseline) and 1 hour, 10 hours, 24 hours and 48 hours after infusion. Depending on the type of factor IX product (e.g. prolonged half-life) sampling time points should be adjusted to cover the main parts of the activity time profile and to ensure that up to 5 half-lives are captured. 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 values in the analysis. Preferably, the testing should be conducted in a central laboratory to decrease variability in test results.

4.4.3. Efficacy and immunogenicity testing

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 III and if there is any suspicion of inhibitor (see also chapter 5.3). In accordance with the requirements for the ≥12 years 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 (high/low titre, bleeding events), 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 using the modified Nijmegen assay. Plasma samples from patients who are suspected or confirmed to have inhibitors should be stored for possible future testing.

Within the application for marketing authorisation, pharmacokinetic data (incremental recovery, $t_{1/2}$, AUC and clearance) as well as the completed efficacy and safety trial in 20 children (0 to <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 pre-authorisation study in children <12 years is finished.

4.5. Clinical investigation in PUPs

Previously untreated patients (PUPs) are defined as those patients who have never been treated with coagulation factor products (except previous exposure to blood components). The concurrent availability and development of many therapeutic products for haemophilia treatment decreases the availability of previously untreated patients for clinical trials, suggesting that informative studies performed in a meaningful number of PUPs will not be feasible in a timely manner. Therefore, formal PUP studies are no longer required; however, every PUP should be closely monitored with regards to treatment performance and inhibitor development through a well-defined and well-managed disease registry. See chapter 8. Risk Management Plan.

5. Change in the 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)).

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. 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 determined on a case-by-case basis depending on the anticipated impact of the changes. Depending on the results from quality and/or non-clinical comparison, clinical data investigating the impact on pharmacokinetics, efficacy and safety could be necessary. The extent of clinical data needed cannot be defined a priori but will be a case-by-case decision.

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 an 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.

6. Risk management and post-marketing investigation

6.1. Risk management plan

This chapter provides specific guidance on topics to be addressed in a RMP for factor IX products. The RMP should be tailored appropriately for the specific product based on the accumulated data from the development programme up to the application for marketing authorisation, taking into account the general guidance on RMPs. This section indicates aspects that would be appropriate to include in the RMP but should not be interpreted as exhaustive. The following points should be considered in the relevant sections of the RMP for new factor IX products as well as for factor IX products with a significant change in the manufacturing process.

RMPs should be compiled in compliance with the provisions of the GVP Module V – Risk Management Systems. The protocol of the post-marketing investigation should be included in the respective annex of the RMP.

6.1.1. Inhibitor formation

The most serious complication of replacement therapy is the development of inhibitors 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 as a cumulative report in RMP Annex VII, including:

- Source of inhibitor reports (e.g. clinical trial/post-authorisation investigation/spontaneous reports)

- Low and high titre, transient 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. Transient inhibitors are 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.
- Classification of risk to develop factor IX inhibitor:
  - Haemophilia severity
  - Status of treatment (i.e. PUP/PTP)
  - Cumulative exposure to factor IX products (total ED and ED on product)
  - Type of gene mutation
  - Age at first treatment
  - Intensity of treatment
- Inhibitor incidence should be expressed as point estimate and 95 % CI.
- 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 product should be discussed separately. This is particularly relevant for products with a significant change in the manufacturing process. The switch from "pre-change" to "post-change" product should be investigated carefully.

6.1.2. 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 reported.

6.1.3. Hypersensitivity/anaphylactic reactions

Hypersensitivity and anaphylactic reactions including against host cell proteins, excipients and residues used in the manufacturing process may occur. These reactions should be classified according to local and systemic hypersensitivity reactions. Patients developing anaphylaxis should be carefully investigated and followed-up for inhibitor development. An appropriate questionnaire/reporting form should be used with information collected on status of treatment (e.g. PUP/PTP). Data on relevant antibodies against factor IX (using appropriate methods), e.g. IgE, IgG, should be submitted. The questionnaire forms should be attached in the RMP in Annex 4.

6.1.4. Thrombogenicity

Thrombotic events need to be monitored and reported. Appropriate questionnaire follow-up forms should be available and questionnaire attached to RMP Annex 4 also.

6.1.5. Measurement of plasma factor IX levels significantly affected by the assay used for clinical monitoring

Where there can be discrepant assay results depending on the assay used for clinical monitoring (see 6.1.1), some information will be included in the product information but other approaches may also be needed including educational material for training of clinical laboratories. The RMP is an appropriate place to address the risk of discrepant monitoring of plasma levels and the measures to avoid this.

6.2. Post-authorisation safety and efficacy studies

In order to collect additional clinical data and to ensure consistency in the long-term between the outcome from pre-authorisation clinical studies and from routine use, a post-marketing investigation should be performed. The clinical study protocol should be submitted with the application for marketing authorisation as part of the RMP (see GVP module V – Risk Management Systems). The results of the pre-authorisation studies should be taken into account for the design of the post-marketing study. Besides aspects like the general product safety and clinical efficacy, there has to be a focus on immunogenicity, particularly on inhibitor development, anaphylactic reactions and thrombogenic effects.

In general, the study should reflect the intended patient population from the countries where the product is intended to be marketed. A detailed patient documentation (diary, logbook, etc.) covering the last 50 EDs or the last 2 years per patient to confirm treatment modality (i.e. prophylaxis, on demand or recent surgery) is needed as a prerequisite for patient enrolment 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 typically needed in a post-marketing study with a factor IX product to cover especially immunogenicity aspects (besides general efficacy and safety) 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 (>150 EDs), and could be recruited regardless of their age, however, aiming for a balanced age distribution. In general, all patients from pre-authorisation clinical trials could be enrolled in post-marketing investigations, previously untreated patients may be included.

The post-marketing investigation protocol will be approved at marketing authorisation as part of the RMP. Information on study progress should be provided with each PSUR and a separate progress study report should be provided to the relevant Competent Authority(ies) 2 years after marketing authorisation to allow for evaluation of recruitment status, progress and the adherence to timelines. The post-marketing investigation should be completed within 4 years respectively prior to 5-year renewal procedure.

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

6.3. Registries

In order to complement information derived from clinical studies in PTPs required for marketing authorisation, every patient suffering from haemophilia, both PUPs and PTPs should be offered to enrol in disease specific registries.
Since a variety of haemophilia registries exist at national and international level, a core set of parameters is essential and is proposed thereafter to allow for potential data merging and analysis.

The following table provides an overview on the core data elements required to be collected in registries. The table is part of an agreed outcome of the haemophilia registries workshop from 2018, organised by EMA and with participants of various stakeholder groups (see references).

Table 1: Core data elements and additional data elements specific for non-replacement therapy:

Core Data Element Category	Core Data Elements Required
Administrative information	• Registry
	• Center
Demographic information	• Patient Identifier
	• Date of birth
	• Gender
Anamnestic information	• Type of haemophilia
	• Severity of haemophilia (% Factor activity)
	• Date of diagnosis of haemophilia
	• Family history of haemophilia/inhibitor (yes/no)
	• Risk factors (e.g. FVIII gene mutation)
Haemophilia treatment information (each treatment)	• Date of treatment
	• Number of exposure days since start of treatment
	• Weight
	• Product
	• Treatment regimen/modality (on demand/prophylaxis)
	• Dose
	• Treatment reason (e.g. surgery, trauma, pain)
	• Bleeding (yes/no), if yes
	• Reason
	• Location
	• Severity
	• Follow-up treatment
Inhibitor information (each measurement)	• Date of measurement
	Titre (BU/mL)
	• Assay description (e.g. Nijmegen, Bethesda, ELISA)
Relevant information on concomitant events (e.g. infections, allergic reactions)	• Date of event onset
	• Event description
	• Date event resolved

Depending on the type of factor concentrate, more data may be required, e.g. for pegylated products long-term measurement of renal and hepatic function (e.g. creatinine) will be important. The above listed core data set should be used for data collection in PUP primarily but is also applicable for PTP.

In order to investigate other important aspects in haemophilia treatment (e.g. demographical change, treatment optimisation) more parameters might be considered.

7. References

Core SmPC for human plasma derived and recombinant coagulation factor IX products

Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products (EMA/CHMP/BPWP/144533/2009 rev. 2)

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

ICH E8 (R1) Note for Guidance on General Considerations for Clinical Trials (CPMP/ICH/291/95)

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

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

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)

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)

Guideline on registry-based studies (EMA/426390/2021)

Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation (EMA/CHMP/564424/2021)

GVP module V – Risk Management Systems

Haemophilia registry workshop held in 2018: (https://www.ema.europa.eu/en/events/haemophilia-registries-workshop

Peyvandi F., Makris M., Collins P., Lillicrap D., Pipe SW., Iorio A., Rosendaal FR., for the Subcommittee on Factor VIII, Factor IX and Rare Coagulation Disorders. Minimal dataset for post-registration surveillance of new drugs in hemophilia: communication from the SSC of the ISTH. J Thromb Haemost 2017; 15: 1878–81

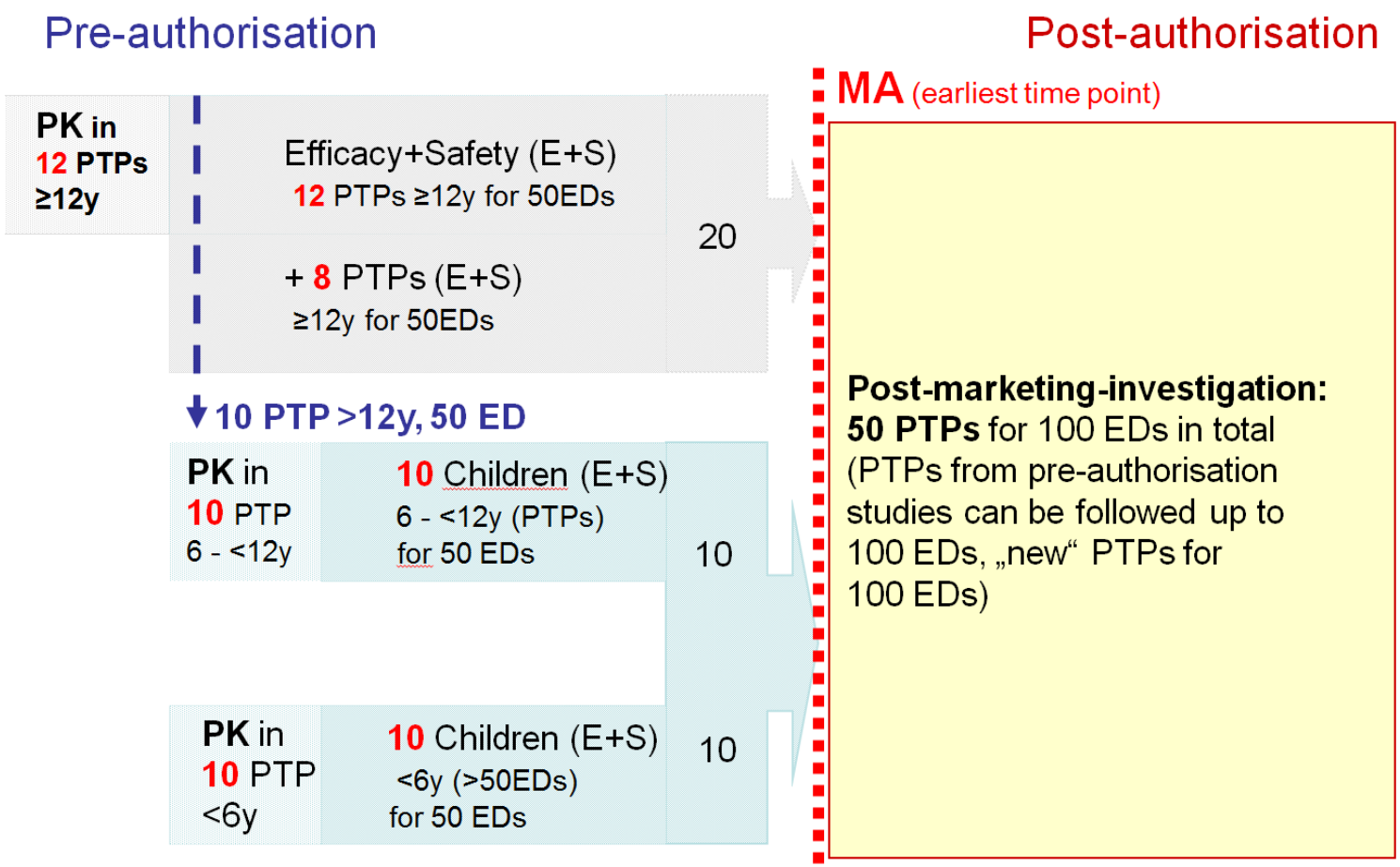
Report of Expert Meeting on Factor VIII Products and Inhibitor Development, 28 February 2006 – 02 March 2006 ((EMEA/CHMP/BPWP/123835/2006) Microsoft Word - Report of Expert Meeting on Factor VIII products and inhibitor development .doc (europa.eu)

Neugebauer B., Drai C., Haase M., Hilger A., Keller-Stanislawski B., Laitinen-Parkkonen P., Mentzer D., Rasmussen C., Ratignier C. and Seitz R. (2008), Factor VIII products and inhibitor development: concepts for revision of European regulatory guidelines. Haemophilia, 14: 142–144. doi: 10.1111/j.1365-2516.2007.01604.

Workshop report: Characterisation of new clotting factor concentrates (FVIII, FIX) with respect to potency assays used for labelling and testing of post infusion samples, 28-29 November 2013 (EMA/135928/2014)
Workshop report: Characterisation of new clotting factor concentrates (FVIII, FIX) with respect to potency assays used for labelling and testing of post infusion samples (europa.eu)

Dodt, J., Hubbard, A. R., Wicks, S. J., Gray, E., Neugebauer, B., Charton, E. and Silvester, G. (2015), Potency determination of factor VIII and factor IX for new product labelling and postinfusion testing: challenges for caregivers and regulators. Haemophilia. doi: 10.1111/hae.12634

Annex I – Overview on clinical trial concept



Annex II – Clinical trials with factor IX products: new products

Trial, subject	Investigation	Parameters
PTP ≥12y study – pre-authorisation		
12 haemophilia B patients (PTP ≥12 years; factor IX ≤2%) without inhibitors and not actively bleeding	Pharmacokinetics[2]	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 (PTP ≥12 years; factor IX ≤2%) 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, 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 < 12y 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 (>50 EDs, <**6y**; factor IX ≤2%) without inhibitors and not actively bleeding	Pharmacokinetics	Incremental recovery, half-life, AUC, clearance.
	Safety	Blood pressure, heart rate, temperature, respiratory rate and adverse events. Thrombogenicity.

[2] In order to allow for evaluation of a patient's individual response, pharmacokinetic information e.g. existing PK data with the patient's previous factor IX product (at least historical or recent recovery and half-life) should be available prior to first administration of the new factor IX product.

Trial, subject	Investigation	Parameters
Multicentre trial in 20 children with haemophilia B allocated to 2 cohorts of 10 PTPs (6 - <12y) and 10 children (<6y, >50EDs)	Clinical efficacy	Factor IX consumption, physician's assessment of response in treatment of major bleeds.
	Immunogenicity	Inhibitor testing immediately before first exposure, ED10-15, ED50-75 and if there is any suspicion of inhibitor development. Continue until 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 III.

Annex III – Post-marketing investigation

Inclusion criteria

- Diagnosis: haemophilia B
- Factor IX activity: ≤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 the relevant Competent Authority(ies).
- Immunocompetent with CD4 lymphocytes >200/µl, HIV negative or having a viral load <200 particles/µl ~ 400000 copies/ml

Documentation of Patient's characteristics

- Gene defect
- Family history of haemophilia
- History of inhibitors
- The viral status of patients should be documented. The patients should be HIV 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
- 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).
- A separate progress study report should be provided to the relevant Competent Authority(ies) 2 years after marketing authorisation to allow for evaluation of recruitment status, progress and the adherence to timelines.
- The post-marketing investigation should be completed within 4 years.

Study procedures

- 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

†baseline inhibitor testing prior to first infusion of test product

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). Inhibitor questionnaires/report forms should be used. 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, 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.