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

Draft

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This guideline (EMA/CHMP/BPWP/144533/2009 rev. 1) replaces guideline with reference number EMA/CHMP/BWP/144533/2009.

Changes from the previous guideline are indicated by underlined text and strike through; the public consultation is restricted to these changes.

Comments should be provided using this template. The completed comments form should be sent to BPWPsecretariat@ema.europa.eu

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GLOSSARY

AUC – Area under the Curve

BU - Bethesda Unit

CI – Confidence Interval

E - Efficacy

ED - Exposure Day

HAART - Highly active anti-retroviral therapy

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 to be documented when an application for a marketing authorisation for recombinant or human plasma-derived factor VIII products is made for use in treatment and prevention of bleeding in patients with haemophilia A. The guidance 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.

Timeline 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 guidance to have separate documents: The Guideline on clinical investigation of recombinant and plasma derived factor VIII products (EMA/CHMP/BPWP/144533/2009) and the Guideline on clinical investigation of recombinant and plasma derived factor IX products (EMA/CHMP/BPWP/144552/2009). EMA/CHMP/BPWP/144533/2009 came into effect on 1 February 2012. Revision 1 is a rapid revision following the 2013 EMA/EDQM workshop on potency assays. The opportunity is taken to make 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 VIII products.

In plasma, factor VIII occurs as a heterodimer, consisting of a light chain (domains A3, C1 and C2), and a heavy chain (domains A1 and A2) and domain B.

The occurrence of an antibody against factor VIII, a so-called inhibitor, is the most important complication in haemophilia treatment. Inhibitors occur in up to about 30% of previously untreated patients (PUP) with severe haemophilia A, usually within the first 100 exposure days.

These inhibitors have mainly been observed in previously untreated children, and approximately one third disappeared on continued treatment with the same product. It now appears that in cases in which inhibitors occur in PUP, patient related factors (certain types of mutations in the factor VIII gene, the family history, ethnicity, possibly HLA-DR constitution) appear to be important determinants of inhibitor development. Patients treated with factor VIII products should be carefully monitored for the development of inhibitory antibodies by appropriate clinical observations and laboratory test.

Two inhibitor ‘outbreaks’ occurred in the early 1990’s in previously tolerant patients who had been treated for a number of years following exposure to plasma-derived factor VIII products subjected to a modified virus inactivation method. Hence, the incidence of inhibitor formation may be affected by the specific product used for treatment and its potential for alteration of factor VIII molecules and generation of ‘neoantigens’.

An EMA expert meeting on factor VIII products and inhibitor development was held in 2006 to provide a forum with experts from EU, USA, Japan and Canada, representatives from the International Society for Thrombosis and Haemostasis (ISTH), the World Health Organisation (WHO), patient organisations and industry to discuss the international standardisation and harmonisation of requirements for clinical studies on factor VIII inhibitor development in haemophilia A patients. The objective was to provide

expert advice on the collection of meaningful and comparable clinical data on the immunogenicity of recombinant and plasma-derived factor VIII products in the future. The outcome of this meeting has been taken into account for the guidance provided within this document[1].

It was agreed upon that the risk of inhibitor formation related to an individual product should be evaluated in previously treated patients (PTPs) since patients with a high degree of previous exposure should be immunotolerant to factor VIII and are considered to be a better suited study population. Nevertheless, depending on the type of factor VIII product (see chapter 6.6) PUP studies should be performed to investigate efficacy and safety in this specific patient population. Clinical trial data, addressing efficacy and safety with respect to immunogenicity 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 recombinant and plasma-derived factor VIII 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).

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 an EMA scientific advice procedure.

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 VIII products are found in Annexes I to III.

2. Scope

The guideline covers clinical investigations to be conducted pre- and post-marketing authorisation. 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. Efficacy: General aspects

Efficacy needs to be demonstrated in clinical trials to be conducted before marketing authorisation combined with the commitment to perform (a) post-authorisation investigation(s) to collect additional

[1] Report of Expert Meeting on Factor VIII Products and Inhibitor Development (EMEA/CHMP/BPWP/123835/2006) and publication in Haemophilia (see References)

clinical data and to bridge in the long-term between the outcome from clinical trials and from routine use. When clinically evaluating human plasma-derived or recombinant coagulation factors for the treatment of haemophilia A, 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 VIII product. Furthermore, clinical efficacy of factor VIII treatment (e.g. prophylaxis, on demand) should be assessed during a period of a minimum of 50 exposure days by the patients themselves and treating physicians.

5. Safety: General aspects

Safety aspects of factor VIII 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.

5.1. Adverse events

Safety, including vital signs, should be assessed in all patients receiving the factor VIII product during clinical trials. All adverse events in clinical studies must be recorded and analysed with regard 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.

The occurrence of neutralising antibodies to factor VIII (see chapter 5.3), which is a major complication in haemophilia A treatment, is considered to be a serious adverse event (SAE) and should be recorded and reported as such, using the category “Important Medical Event” and any other applicable. This requirement should be included in all study protocols.

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.

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 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 VIII 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 TSE and other emerging pathogens. Manufacturers should follow the respective guidance

documents and position statements. Information can be found in the Biologicals 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 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.

5.3. Immunogenicity

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

The occurrence of antibodies against factor VIII is a major complication of haemophilia A treatment. The risk of inhibitor occurrence is higher in patients with severe haemophilia A than in patients with moderate and mild disease and also the genotype (high risk: inversions, large deletions or nonsense mutations of the factor VIII gene) and ethnic background of the patient is relevant. In addition risk may be associated with commencing treatment in previously untreated patients or with changing of treatment or where the antigenicity of the product has been altered due to changes in the manufacturing process. Previously treated patients are the most suitable candidates to test the product-related immunogenicity of a factor VIII product. The diagnosis of a factor VIII inhibitor will be based on clinical observations and be confirmed by factor VIII inhibitor testing in the laboratory.

Neutralising antibodies are the most important immunological concern and therefore the following aspects and basic principles should be considered:

- Inhibitor development should be studied in previously treated patients (>150 exposure days, suffering from severe haemophilia A with a factor VIII level < 1%);
- The modified Nijmegen method of the Bethesda assay should be used. Validated testing should be performed in a central laboratory;
- In case of positive results for an inhibitor, an inhibitor retesting using a second separately drawn sample as confirmatory measurement should be performed in a central laboratory. The sampling timepoints should be recorded and included in the SAE report.
- The definitions for thresholds are ≥0.6 BU for “a low titre” inhibitor and >5 BU for a ‘high-titre’ inhibitor.
- Preferably, inhibitor testing should be performed when factor VIII level has reached baseline.
- Conditions influencing factor VIII inhibitor measurements should be screened and documented, like chronic viral infections (e.g. HIV, HCV) or Lupus anticoagulant;

- Detailed patient characteristics should be recorded (e.g. ethnicity, family history, life style, general health status, infection status, type of factor VIII gene mutation, reason for treatment, treatment start date, kind of treatment (on demand, prophylactic, continuous infusion)).
- Recovery should be monitored.

See section 8 for further aspects to be considered.

6. Application for marketing authorisation: "New products"

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

6.1. General aspects on clinical trials

In view of the limited availability of patients suffering from haemophilia A, data from pre-licensing studies only are considered insufficient to estimate all aspects of therapy with factor VIII 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. The number of patients typically needed to be enrolled into the pre-authorisation clinical trials is 100. This number has been selected by balancing the clinical data package needed to demonstrate efficacy and safety against the availability of patients suffering from a rare disease. The number of patients is expected to be adequate to provide relevant information on general safety aspects and to demonstrate efficacy of a factor VIII product in terms of its ability to restore factor VIII levels and reach haemostasis, to stop as well as to prevent bleeding. In view of the limited number of patients in the pre-authorisation trials, further information mainly focussing on safety aspects is needed through post-marketing investigations. In case inhibitors occur at an incidence of 1.5% or higher, there is at least 95% probability to observe antibodies in one or more patients in a cohort of 200 patients.

The clinical development for factor VIII 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 PTPs ≥12 years of age. Subsequently, when PK and efficacy/safety data from 20 PTPs ≥12 years for at least 50 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 50 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.

A PUP study needs to be conducted for all novel recombinant factor VIII products, such as novel genetic constructs or modifications of the factor VIII molecule in order to alter its *in vivo* properties, e.g. pharmacokinetics, and for factor VIII products manufactured with novel production methods, e.g. a new cell line where there is limited experience. ~~Pups are excluded from the indication~~ The lack of data in PUPs should be indicated through a statement in 4.2. Posology and method of administration (see core SmPC) until data from 50 PUPs investigated for efficacy and safety for at least 50 EDs each are available. In the case of plasma-derived factor VIII products (e.g. manufactured with novel methods), the need for PUP studies will be considered on a case by case basis. Applicants will receive feedback on this issue when submitting the paediatric investigation plan or waiver application and may also seek scientific advice from the EMA to clarify this issue.

Please refer to Annex I 'Overview on clinical trial concept' and Annex II 'Clinical trials for factor VIII products: new products'.

6.1.1. Potency measurements

The potency assignments for factor VIII products covered by European Pharmacopoeia (Ph. Eur.) monographs have to be performed with the Ph. Eur chromogenic assay. However, 'with the agreement of the competent authority, alternative methods of analysis may be used for control purposes, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used.'[2].

A number of different assays for factor VIII potency measurement are available. For some products significantly different product potencies can be obtained with the different methods/assays, reagents and reference standards that are available. Significant discrepancies between the Ph. Eur. chromogenic assay and thromboplastin time (aPTT)-based one stage clotting assay have been observed. Furthermore, when using an aPTT-based one stage clotting assay, factor VIII activity results can be significantly affected by both the type of aPTT reagent and the reference standard used in the assay. 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 ISTH has published "Recommendations on the potency labelling of factor VIII and factor IX concentrates".[3] 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 characterization of new factor VIII products, taking into account ISTH recommendations, in a variety of potency assays against the WHO IS (concentrate and plasma) is important. In the case that 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 comparison of in vitro and in vivo functionality. Consequences for laboratory monitoring of product plasma levels should be addressed in the risk management plan and appropriate information should be given to users of the product.

6.2. Efficacy in PTPs ≥12 years

Pharmacokinetics

A pharmacokinetic trial should be performed in at least 12 PTPs (>150 EDs) suffering from severe haemophilia A (factor VIII <1%) and who are immunocompetent (HIV patients should have CD4 > 200/µL). 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 VIII product for at least 4 days. In order to allow for evaluation of a patient's individual response, existing pharmacokinetic information with the patient's previous factor VIII product (historical or recent recovery and half-life) should be available prior to first administration of the new factor VIII product. Samples should be taken before injection of 25-50 IU/kg of the factor VIII product (baseline), 10-15 minutes (times refer to the

[2] European Pharmacopoeia, General Notices. In: European Pharmacopoeia, 8th edition, Strasbourg, France, European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe, 2015.
[3] Recommendations on the potency labelling of factor VIII and factor IX concentrates (Hubbard AR, Dodt J, Lee T, Mertens K, Seitz R, Srivastave 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).

interval after the completion of the infusion) and at 30 minutes, and 1 hour. Additional time points to include 3, 6, 9, 24, 28, and 32 hours post infusion; a 48 hour sample is optional provided the patient was given at least 50 IU/kg. Depending on the type of factor VIII product (e.g. prolonged half-life) sampling time points may be adjusted to cover the main parts of the activity time profile. At least 3 different lots should be employed in the trial. Incremental recovery is determined as the peak factor level recorded in the first hour after infusion and is reported as [IU/ml]/[IU/kg]. According to the European Pharmacopoeia monograph for human coagulation factor VIII, potency assignments for factor VIII products have to be performed with the chromogenic assay. 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.

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

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

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

Efficacy including surgery

Clinical efficacy of factor VIII should be evaluated in at least 50 PTPs (≥12 years, >150 EDs), suffering from severe haemophilia A (factor VIII <1%), and who are immunocompetent (HIV patients should have 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 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 VIII 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 be assessed by calculating the consumption of factor VIII, 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 continuous infusion therapy is claimed, the study should be carried out in at least 12 severe haemophilia A patients (factor VIII <1%) 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 VIII 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.

Immune tolerance induction

Immune tolerance induction is not a subject of this guideline.

6.3. Clinical investigation in PTPs ≥12 years

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 ≥12 years of age, with a factor VIII level <1% 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. At least 50 patients should be followed and documented for a minimum of 50 exposure days. These data should be provided with the application.

Immunogenicity testing

The factor VIII 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 VIII 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 Nijmegen modification of the Bethesda assay. Plasma samples from patients who are suspected of inhibitors or who have developed inhibitors should be stored until the 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.

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.

6.4. Clinical investigation in children <12 years

Since children may respond differently compared to adults, a multicentre trial should include at least 50 children allocated to two age cohorts. A minimum of 25 patients should be PTPs at the age of 6-<12 years and at least 25 patients should be <6 years who have undergone >50 EDs with previous factor VIII products. The clinical trial in children < 12 years should not start before safety is proven for 50 EDs each of 20 patients who are included in the PTP trial ≥12 years.

The clinical trial in children should begin with the investigation of pharmacokinetics (incremental recovery, *in vivo* half-life, AUC and clearance) in 12 patients of each age cohort. In order to allow for evaluation of a patient's individual response, existing pharmacokinetic information with the patient's previous factor VIII product (historical or recent recovery and half-life) should be available prior to first administration of the new factor VIII product. With regard to patient compliance, PK sampling time points can be reduced to measurements prior to infusion (baseline) and 1 hour, 10 hours, 24 hours and 48 hours after infusion. Depending on the type of factor VIII 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 VIII 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 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, 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, *in vivo* half-life, AUC and clearance) as well as the completed efficacy and safety trial in 50 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 a balanced age distribution can be achieved (approximately 60 patients <12 years out of 200 patients). Furthermore, patients <12 years can only be enrolled in the post-marketing investigation when the pre-authorisation study in children <12 years is finished.

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 VIII product (e.g. novel modified recombinant proteins to extend half-life). For plasma-derived factor VIII products, the need to perform PUP studies will be considered if novel manufacturing methods are used, on a case by case basis. For novel factor VIII products where a PUP study is required, the PUP study should start prior to marketing authorisation and the lack of data in PUPs should be indicated through a statement in 4.2 Posology and method of administration (see core SmPC), ~~, however, PUPs will be excluded from the indication~~ until data from 50

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 50 PUPs evaluated for efficacy and safety during at least 50 ED connected with a post-approval commitment to follow up at least 100 PUPs (50 from efficacy/safety trial and 50 new) for a minimum of 100 ED.

The clinical trial in PUPs should be started when data are available from 20 patients participating in the children trial <12 years with 50 ED each, including a minimum of 10 patients <6 years, and when pharmacokinetic investigations in children <12 years are completed.

6.6. Post-marketing investigation

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 risk management plan (see Volume 9A of The Rules Governing Medicinal Products in the European Union). 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 and respective data. The general principles of immunogenicity and inhibitor documentation as laid down in chapter 5.3 should be taken into account.

In general, 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 either the last 50 exposure days or the last 2 years per patient to confirm treatment modality (i.e. prophylaxis, on demand or recent surgery) is needed as a pre-requisite 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 number of patients typically needed in a post-marketing study with a factor VIII product to cover especially immunogenicity aspects (besides general efficacy and safety) is 200. In case of plasma-derived factor VIII 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 provided that a balanced age distribution can be achieved (e.g. 60 patients <12 years out of 200 patients). In case inhibitors occur at an incidence of 1.5% or higher, there is at least 95% probability to observe antibodies in one or more patients in a cohort of 200 patients.

In general, all patients from pre-authorisation clinical trials could be enrolled in post-marketing investigations.

The post-marketing investigation protocol will be approved at marketing authorisation as part of the risk management plan. 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.

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

7. 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)).

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 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).

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.

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 “pre-change” product versus the “post-change” product should be performed in at least 12 PTPs suffering from haemophilia A (factor VIII <1%). 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 VIII product for at least 4 days. Samples should be taken before injection of 25-50 IU/kg of the factor VIII product (baseline), 10-15 minutes (times refer to the interval after the completion of the infusion) and at 30 minutes, and 1 hour. Additional time points to include 3, 6, 9, 24, 28, and 32 hours post-infusion; a 48 hour sample is optional

provided the patient was given at least 50 IU/kg. Depending on the type of factor VIII product (e.g. prolonged half-life) further sampling points could be necessary. A minimum of 3 different lots of the "post-change" product should be employed in the trial. Incremental recovery is determined as the peak level recorded in the first hour 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 and requirement for transfusion.

8. Risk management plan

This chapter provides specific guidance on topics to be addressed in a Risk Management Plan (RMP) for factor VIII products. The requested information is mainly based on the gaps in information identified following the class review for recombinant factor VIII 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 Risk Management Plan for new factor VIII products as well as for factor VIII products with a significant change in the manufacturing process.

Risk Management Plans should be compiled in compliance with the provisions of Volume 9A of The Rules Governing Medicinal Products in the European Union. The protocol of the post-marketing investigation should be included in the respective annex of the RMP.

Inhibitor formation

The most serious complication of replacement therapy with factor VIII is the development of factor VIII inhibitors in PUPs and PTPs. 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, 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.)
- Type 1 and 2 inhibitors
- Classification of risk to develop factor VIII inhibitor:
  - Haemophilia severity
  - Status of treatment (i.e. PUP/PTP)
  - Cumulative exposure to factor VIII products (total ED and ED on product)

- Type of gene mutation
- Ethnicity
- 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 VIII product 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.

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.

Hypersensitivity / anaphylactic reactions

Hypersensitivity / 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 VIII (using appropriate methods), e.g. IgE, IgG, should be submitted.

Measurement of plasma factor VIII 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 Risk Management Plan is an appropriate place to address the risk of discrepant monitoring of plasma levels and the measures to avoid this.

References

Report of Expert Meeting on Factor VIII Products and Inhibitor Development, 28 February 2006 – 02 March 2006 (EMEA/CHMP/BPWP/123835/2006), http://www.ema.europa.eu/docs/en_GB/document_library/Report/2009/11/WC500015512.pdf

European Pharmacopoeia, 8th edition, Strasbourg, France, European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe, 2015.

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.x

Core SmPC for Human Plasma Derived and Recombinant Coagulation Factor VIII Products

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)

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/07/WC500169760.pdf

https://www.edqm.eu/en/Workshop-on-characterisation-of-new-clotting-factor-concentrates-new-report-available-1582.html?mbID=216

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

Applicants should also refer to other relevant European and ICH guidelines (in their current version) including those on:

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

ICH E8 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),

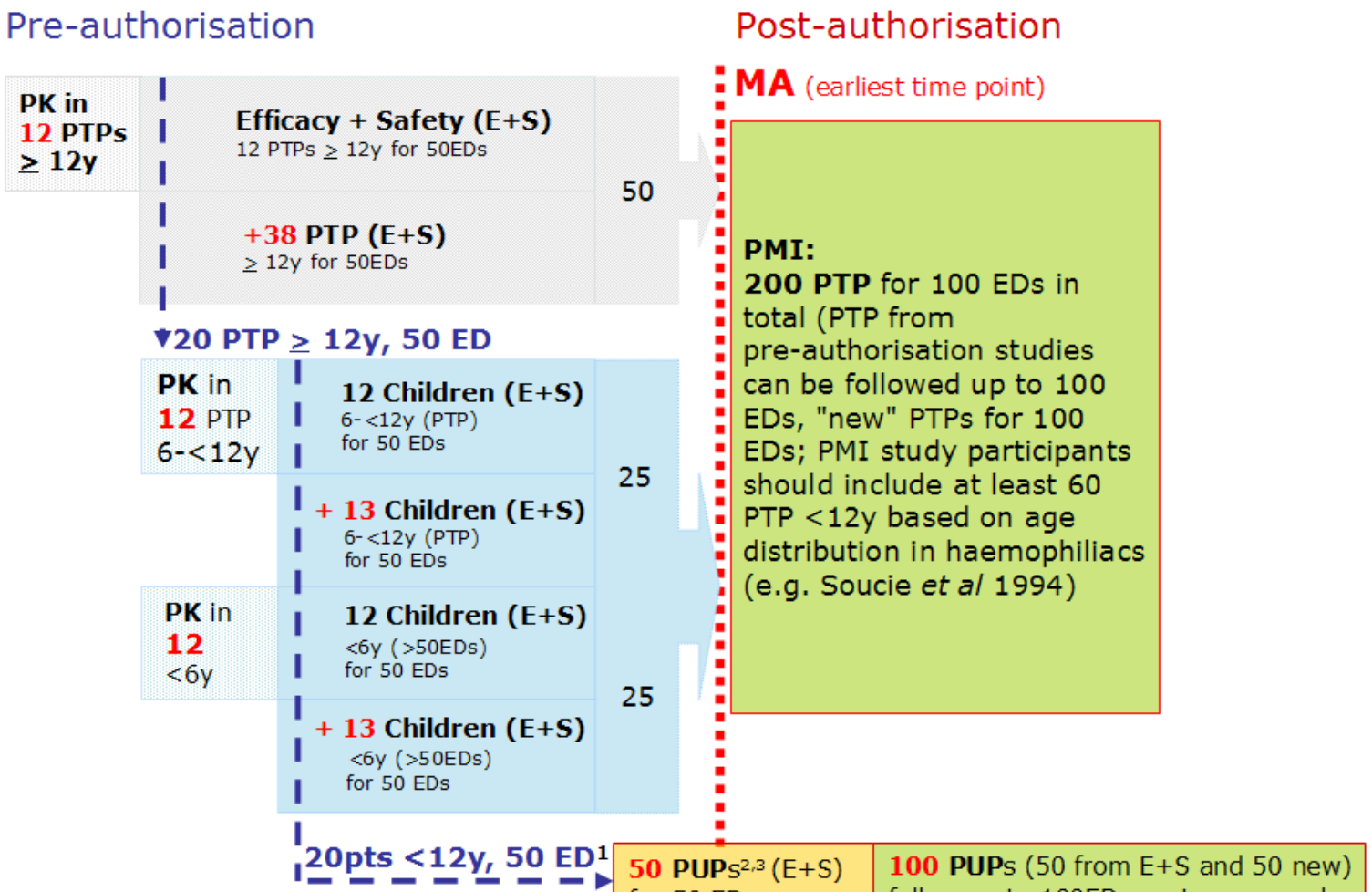
Guideline on comparability of biotechnology-derived medicinal products after a change in the manufacturing process - non-clinical and clinical issues (EMEA/CHMP/BMWP/101695/2006),

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), and

Volume 9A of The Rules Governing Medicinal Products in the European Union: RMP

Annex I – Overview on clinical trial concept



[1] min. 10 patients <6y and pk in children 0-<12y completed
[2] plasma-derived factor VIII products = case by case
[3] completion of clinical study in 50 PUPs not required for initial MAA however for approval of indication in PUPs for novel products

SmPC of novel products: Indication is restricted as in 4.2 of core SmPC until data from 50 PUPs (E+S) are available.

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

Trial, subject	Investigation	Parameters
PTP ≥12y study – pre-authorisation		
12 haemophilia A patients (PTP ≥12 years; factor VIII <1%) without inhibitors and not actively bleeding	Pharmacokinetics[4]	Incremental recovery, half-life, AUC, clearance. Patients should be re-tested after 3-6 months (including factor VIII inhibitor assay).
	Safety	Blood pressure, heart rate, temperature, respiratory rate and adverse events.
5 haemophilia A patients (PTP ≥12 years; factor VIII <1%) undergoing at least 10 surgical procedures	Clinical efficacy	Efficacy of haemostasis, loss of blood and requirement for transfusion. Factor VIII consumption.
	Safety	Adverse events.
Efficacy and safety in 50 PTPs (≥12 years; factor VIII <1% and CD4>200/µl)	Clinical efficacy	Factor VIII consumption, physician's assessment of response in treatment of major bleeds.
	Immunogenicity	Inhibitor titre in Bethesda Units, using the Nijmegen modification of Bethesda assay, 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.
Children <12y study – pre-authorisation (to be started after results of 50 ED in 20 PTPs (≥12 years) have become available)		
12 haemophilia A patients (PTPs, **6 - <12y**; factor VIII <1%) without inhibitors and not actively bleeding 12 haemophilia A patients (>50 EDs, <**6y**; factor VIII <1%) without inhibitors and not actively bleeding	Pharmacokinetics	Incremental recovery, half-life, AUC, clearance.
	Safety	Blood pressure, heart rate, temperature, respiratory rate and adverse events
Multicentre trial in 50 children with haemophilia A allocated to 2 cohorts of 25 PTPs (6 - <12y) and 25 children (<6y, >50EDs)	Clinical efficacy	Factor VIII 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

[4] 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 VIII product (at least historical or recent recovery and half-life) should be available prior to first administration of the new factor VIII product.

Trial, subject	Investigation	Parameters
		until a minimum of 50 exposure days
	Safety	Adverse events.
Post-marketing investigation		
200 PTPs for 100 EDs in total (PTPs from pre-authorisation studies can be followed up to 100 EDs, "new" PTPs for 100 EDs; post-marketing investigation participants should include e.g. 60 PTPs <12y based on age distribution in haemophiliacs	Clinical efficacy Immunogenicity Safety	Protocol should be provided according to Annex III.
PUP study (novel products) (to be started after results of 50 ED in 20 children (0 - <12y, at least 10 of them <6y) are available and PK in children 0 - <12y completed)		
50 PUPs for at least 50 EDs	Clinical efficacy	Factor VIII consumption, physician's assessment of response in treatment of major bleeds.
	Immunogenicity	Inhibitor testing immediately before first exposure, ED10-15, ED50 and if there is any suspicion of inhibitor development. Continue until a minimum of 50 exposure days.
	Safety	Adverse events, blood pressure, heart rate, temperature.
Post-approval commitment of PUP indication 100 PUPs should be followed up to 100 EDs (50 PUPs from pre-approval PUP indication can be followed up to 100 EDs, 50 "new" PUPs for 100 EDs)		

Annex III – Post-marketing investigation

Inclusion criteria

- Diagnosis: haemophilia A
- Severity: <1% factor VIII:C[5]
- Number of exposure days before inclusion: >150 ED
- PTPs of every age group could be included, provided that trial in children is finished (PK and efficacy and safety) and report is submitted and evaluated by the relevant Competent Authority(ies). E.g. 60 PTPs <12y should be included in the study.
- 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
- Ethnicity
- 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 200 patients per post-marketing investigation
- Follow-up of each patient must be at least 100ED
- 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)

[5] At least 100 patients <1% should participate. In case patients with up to 2% baseline level are enrolled a separate statistical evaluation for <1% and <2% should be provided.

	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 VIII 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 low 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.