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4 **Guideline on clinical investigation of recombinant and**  
5 **human plasma-derived factor IX products**  
6 **Draft**

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7  
8 This guideline replaces 'Guideline on clinical investigation of recombinant and human plasma-derived  
9 factor IX products' (EMA/CHMP/BPWP/144552/2009 Rev. 1, Corr. 1)

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<b>Keywords</b>	<b><i>Recombinant factor IX, plasma-derived factor IX, efficacy, safety, immunogenicity, inhibitor, thrombogenicity, anaphylactic reactions, potency assays</i></b>
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11 Guideline on the clinical investigation of recombinant and  
12 human plasma-derived factor IX products

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41 **GLOSSARY**

- 42 AUC – Area under the Curve
- 43 BU - Bethesda Unit
- 44 CI – Confidence Interval
- 45 E - Efficacy
- 46 ED - Exposure Day
- 47 HAART - Highly active anti-retroviral therapy
- 48 IS - International Standard
- 49 ITI – Immune Tolerance Induction
- 50 IU – International Units
- 51 MA – Marketing Authorisation
- 52 MAA – Marketing Authorisation Application
- 53 p-d - plasma-derived
- 54 PhVWP - Pharmacovigilance Working Party
- 55 PK – Pharmacokinetics
- 56 PMI – Post Marketing Investigation
- 57 PTP - Previously Treated Patient (defined as >150 EDs)
- 58 PUP - Previously Untreated Patient
- 59 RMP - Risk Management Plan
- 60 S - Safety
- 61 SAE – Serious Adverse Event
- 62 TSE – Transmissible spongiform encephalopathy
- 63 SmPC – Summary of Product Characteristics
- 64 y - years

## 65 **Executive summary**

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

71 Timeline history of guideline: The original Note for Guidance on Clinical Investigation of Human Plasma  
72 Derived FVIII and FIX Products (CPMP/BPWG/198/95) came into operation on 14 February 1996. The  
73 first revision (CPMP/BPWG/198/95 Rev. 1) came into operation in April 2001. The original Note for  
74 Guidance on Clinical Investigation on Recombinant FVIII and FIX Products (CPMP/BPWG/1561/99)  
75 came into operation in April 2001. Draft revisions of CPMP/BPWG/1561/99 and CPMP/BPWG/198/95  
76 were released for public consultation in July 2007. Following this consultation, it was decided to  
77 reorganise the guidance to have separate documents: The Guideline on clinical investigation of  
78 recombinant and plasma derived factor VIII products (EMA/CHMP/BPWP/144533/2009) and the  
79 Guideline on clinical investigation of recombinant and plasma derived factor IX products  
80 (EMA/CHMP/BPWP/144552/2009). EMA/CHMP/BPWP/144552/2009 came into effect on 1 February  
81 2012. Revision 1 was a rapid revision following the 2013 EMA/EDQM workshop on potency assays. In  
82 July 2015 an EMA workshop on registries in hemophilia came to the recommendation that the clinical  
83 trial concept requiring PUP studies for FIX products needs to be reconsidered. The number of suitable  
84 patients especially previously untreated patients (PUPs) to be enrolled in clinical trials is problematic.  
85 Hence, the conduct of sufficiently informative clinical trials in PUPs to estimate important  
86 characteristics of single products is considered difficult. Following a public consultation in 2017, a  
87 second workshop on haemophilia registries was held on 8 June 2018 which aimed at defining the  
88 requirements for practical implementation using existing registries to support post-authorisation  
89 observational studies of haemophilia medicines. The workshop discussed recommendations on  
90 important aspects such as appropriate governance of registries, patient consent, data collection, data  
91 quality and data sharing, and interoperability between different registries. Therefore the obligation to  
92 perform clinical trials in PUPs for marketing authorisation purposes has been deleted. Furthermore, a  
93 core parameter set for registry data collection in haemophilia is introduced following the workshop on  
94 haemophilia registry in June 2018. The opportunity is taken to make other minor updates.

## 95 **1. Introduction (background)**

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

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

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

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

106 These data are required for:

107 • products for which an application for a marketing authorisation is to be submitted, referred to as  
108 'new products' in the text; and

109 • authorised products where a significant change in the manufacturing process has been made (e.g.  
110 additional viral inactivation/removal steps or new purification procedures).

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

113 Some of the principles (e.g. choice of patients, patients' characteristics, follow up of patients) of this  
114 guideline could also apply for non-replacement products (e.g. monoclonal antibodies, gene-therapy). If  
115 a specific benefit of a certain product should be claimed e.g. a prolonged half-life which might lead to  
116 modifications of the clinical trial, it is recommended that advice on the design of clinical studies is  
117 sought via an EMA scientific advice procedure.

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

## 122 **2. Scope**

123 The guideline covers clinical investigations to be conducted pre- and post-marketing authorisation of all  
124 plasma-derived and recombinant FIX products. In general, quality aspects are outside the scope of this  
125 guideline.

## 126 **3. Legal basis**

127 This guideline has to be read in conjunction with the introduction and general principles (4) and Annex  
128 I to Directive 2001/83/EC as amended, as well as the Paediatric Regulation (EC) 1901/2006 as  
129 amended.

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

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

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

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

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

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

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

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

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

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

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

148 GVP module V – Risk Management Systems

## 149 **4. Efficacy: General aspects**

150 Efficacy needs to be demonstrated in clinical trials to be conducted before marketing authorisation  
151 combined with the commitment to perform (a) post-authorisation investigation(s) to collect additional  
152 clinical data and to bridge in the long-term between the outcome from clinical trials and from routine  
153 use. When clinically evaluating human plasma-derived or recombinant coagulation factors for the  
154 treatment of haemophilia B patients, the initial trial typically examines the pharmacokinetics of the  
155 principal active factor. Appropriate pharmacokinetic data (incremental recovery, half-life, area under  
156 the curve (AUC), and clearance) are the most important surrogate endpoints for efficacy of a new  
157 factor IX product. Furthermore, clinical efficacy of factor IX treatment (e.g. prophylaxis, on demand)  
158 should be assessed during a period of a minimum of 50 exposure days by the patients themselves and  
159 treating physicians.

## 160 **5. Safety: General aspects**

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

### 165 **5.1. Adverse events**

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

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

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

### 175 **5.2. Safety with respect to viruses and other transmissible agents**

#### 176 Recombinant products

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

## 182 Plasma-derived products

183 Manufacturers of plasma-derived products, including factor IX products, are obliged to optimise viral  
184 safety by selection of donors, screening of individual donations and plasma pools for specific markers  
185 of infection and the inclusion of effective steps for the inactivation/removal of viruses in manufacturing  
186 processes. Similar principles to those outlined for viral safety should apply for all transmissible agents  
187 including TSE and other emerging pathogens. Manufacturers should follow the respective guidance  
188 documents and position statements. Information can be found in the Biologicals guidelines on the EMA  
189 website in the section "Guidelines on Plasma-derived Medicinal Products".

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

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

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

### 201 **5.3. Immunogenicity**

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

204 The incidence of inhibitors in haemophilia B patients following administration of factor IX is less  
205 common compared to the incidence found in haemophilia A patients. Inhibitors to factor IX have been  
206 demonstrated in approximately 4% of patients with severe haemophilia B. It has been observed that  
207 the occurrence of inhibitors is commonly associated with the total deletion of the factor IX gene.  
208 However, with regard to investigation of development of antibodies, the basic principles as outlined for  
209 haemophilia A patients in chapter 5.3 of the Guideline on the clinical investigation of recombinant and  
210 human plasma-derived factor VIII products (EMA/CHMP/BPWP/144533/2009 rev. 2) should be taken  
211 into account where applicable. Unlike those with haemophilia A, patients with haemophilia B more  
212 often experience anaphylactic reactions to factor IX products in association with the development of  
213 inhibitors. Literature also reports on the occurrence of anaphylactic type reactions as well as the  
214 development of a nephrotic syndrome following immune tolerance therapy. These problems have been  
215 observed for plasma-derived as well as for recombinant factor IX products.

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

### 218 **5.4. Thrombogenicity**

219 Treatment with plasma-derived factor IX products that contain factors II, VII and X has been  
220 associated with thrombosis. Factor IX products with higher purity have displayed less risk of  
221 thrombogenicity. For new factor IX products, appropriate tests for markers of activation of coagulation  
222 (prothrombin fragment 1+2, thrombin-antithrombin (TAT) and D-dimer) should be carried out in pre-

223 and post-infusion samples obtained in the non-bleeding state. This should be determined in the  
224 patients participating in the pharmacokinetic trial. Clinical evaluation of thrombosis should be  
225 undertaken by safe, objective means in a minimum of 5 patients undergoing at least 10 surgical  
226 procedures. Additional information on other covariates influencing the risk such as obesity, age etc.  
227 might be important.

## 228 **6. Application for marketing authorisation: “new products”**

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

### 231 **6.1. General aspects on clinical trials**

232 In view of the limited availability of patients suffering from haemophilia B, data from pre-licensing  
233 studies only are considered insufficient to estimate all aspects of therapy with factor IX products,  
234 especially with respect to immunogenicity. Therefore, to collect additional clinical data and to ensure  
235 consistency in the long-term between the outcome from pre-authorisation clinical studies and from  
236 routine use, a post-marketing investigation should be performed. The number of patients typically  
237 needed to be enrolled into the pre-authorisation clinical trials is a minimum of 40. This number has  
238 been selected by balancing the clinical data package needed to demonstrate efficacy and safety against  
239 the availability of patients suffering from a rare disease. The number of patients is expected to be  
240 adequate to provide relevant information on general safety aspects and to demonstrate efficacy of a  
241 factor IX product in terms of its ability to restore factor IX levels and reach haemostasis, to stop as  
242 well as to prevent bleeding. In view of the limited number of patients in the pre-authorisation trials,  
243 further information mainly focussing on safety aspects is needed through post-marketing investigations  
244 in registries.

245 The clinical development for factor IX products should follow a stepwise approach in order to have  
246 some experience in adults and older children before investigating younger children. Therefore, the  
247 initial age cohort to be investigated is previously treated patients (PTPs)  $\geq 12$  years of age.  
248 Subsequently, when PK and efficacy/safety in 10 PTPs  $\geq 12$  years for at least 50 EDs are available, the  
249 clinical trial(s) in children 0 - <12 years can be initiated. The clinical study in children of 0 - <12 years  
250 should be started with PK followed by investigation of efficacy and safety for at least 50 EDs each in 20  
251 children. These data have to be provided within the initial application for marketing authorisation. The  
252 clinical investigation in children needs to be supported by an approved paediatric investigation plan.

253 Please refer to Annex I ‘Overview on Clinical Trial Concept’ and Annex II ‘Clinical Trials for Factor IX  
254 Products “New Products”’.

#### 255 **6.1.1. Potency measurement**

256 A number of different assays for factor IX potency measurement are available and for some products  
257 significantly different product potencies can be obtained with the different methods/assays, reagents  
258 and reference standards that are available. These method-related potency discrepancies can impact  
259 both the finished product potency labelling and also the clinical monitoring post-infusion. A working  
260 group of the ISTH has published “Recommendations on the potency labelling of factor VIII and factor  
261 IX concentrates”.<sup>\*</sup> These recommendations include advice for the characterization of products with

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<sup>\*</sup> 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



262 respect to potency assays, calibration of manufacturers' product reference, pharmacokinetic studies  
263 and testing of post-infusion samples. A joint EMA/EDQM workshop on this topic was held in 2013 (see  
264 reference list).

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

## 273 **6.2. Efficacy in PTPs $\geq 12$ years**

### 274 Choice of patients

275 Previously treated patients (PTPs) with at least 150 treatment EDs to previous products are considered  
276 as low risk patients and should be evaluated for product related immunogenicity. These PTPs should be  
277  $\geq 12$  years of age, with a factor IX level  $\leq 2\%$  and immunocompetent (HIV positive patients should  
278 have CD4 lymphocytes  $> 200/\mu\text{l}$ ). The viral status of patients should be documented. The patients  
279 should be HIV negative or have a viral load  $< 200$  particles/ $\mu\text{l}$  or  $< 400000$  copies/ml. Due to the lower  
280 incidence of haemophilia B as compared to haemophilia A, at least 20 previously treated patients  
281 should be followed and documented for a minimum of 50 exposure days. These data should be  
282 provided with the application.

### 283 Pharmacokinetics

284 A pharmacokinetic trial should be performed in at least 12 PTPs ( $> 150$  exposure days (EDs)) suffering  
285 from haemophilia B (factor IX  $\leq 2\%$ ) and who are immunocompetent (HIV patients should have CD4  
286  $> 200/\mu\text{L}$ ) The study should record incremental recovery, terminal half-life ( $t_{1/2}$ ), area under the curve  
287 (AUC), and clearance in patients without inhibitors who are not actively bleeding. Patients should be at  
288 least 12 years of age and should not have received an infusion of any factor IX product for at least 4  
289 days. In order to allow for evaluation of a patient's individual response, existing pharmacokinetic  
290 information with the patient's previous factor IX product (historical or recent recovery and half-life)  
291 should be available prior to first administration of the new factor IX product. Samples should be taken  
292 before injection of 50-75 IU/kg of the factor IX product (baseline), between 10-15 minutes (times refer  
293 to the interval after the completion of the infusion), at 30 minutes, and at 1, 3, 6, 9, 24, 48, and 72  
294 hours post-infusion. Depending on the type of factor IX product (e.g. prolonged half-life) sampling  
295 time points should be adjusted to cover the main parts of the activity time profile, i.e. subsequent to  
296 the 1h sample at least 6 samples should be analysed to capture up to 5 half-lives. At least 3 different  
297 lots should be employed in the trial. Incremental recovery is determined as the peak factor level  
298 recorded in the first hour after infusion and is reported as [IU/ml]/[IU/kg]. As several assay methods  
299 are possible, the assay used should be described. Preferably the same assay should be used for  
300 analysis of the product and the patient's plasma (see also 6.1.1).

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

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Standardisation Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. 2013;  
11:988-9. doi: 10.1111/jth.12167).

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

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

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

#### 312 Efficacy including surgery

313 Clinical efficacy of factor IX should be evaluated in at least 20 PTPs ( $\geq 12$  years,  $> 150$  EDs), suffering  
314 from haemophilia B (factor IX  $\leq 2\%$ ) and who are immunocompetent (HIV patients should have CD4  $>$   
315  $200/\mu\text{L}$ ). During an observation period of a minimum of 50 exposure days, clinical response should be  
316 assessed by the patients. Response should be assessed as "none", "moderate", "good" or "excellent"  
317 by the physician for those patients who were treated in hospital with the product for major bleeds. In  
318 addition, response should be determined by the physician in a minimum of 5 patients undergoing at  
319 least 10 surgical procedures (comprising major surgeries), including efficacy of haemostasis, loss of  
320 blood, and requirements for transfusion. For the assessment of clinical efficacy of factor IX in long-  
321 term prophylaxis, patients should be treated for 6 months and assessed for bleeding episodes,  
322 bleeding intervals and number of treatments.

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

#### 326 Continuous infusion

327 If continuous infusion therapy is claimed, the study should be carried out in at least 10 severe  
328 haemophilia B patients (FIX  $\leq 2\%$ ) undergoing elective major surgical procedures.

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

$$\text{Clearance} \times \text{desired steady state level} = \text{infusion rate (IU/kg/hr)}$$

332  
333 (if necessary plus a corresponding safety margin)

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

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

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

#### 342 Immunogenicity testing

343 The factor IX inhibitor titre should be determined by following the schedule set out in Annex III. In the  
344 clinical studies, it is proposed to perform sampling for inhibitor measurements not less than 3 days  
345 after the previous administration, if possible. Product specific properties e.g. extended half-life should  
346 be taken into account to avoid interference from residual factor IX product. For all patients who  
347 develop inhibitors a full clinical report should be provided including clinical relevance, the cumulative  
348 incidence and the number of exposure days. The titre of the inhibitor should be reported in Bethesda  
349 Units (BU) using the Bethesda assay or the Nijmegen modification of the Bethesda assay. Plasma  
350 samples from patients who are suspected of inhibitors or who have developed inhibitors should be  
351 stored until evaluation of the clinical study by the competent authority is completed in order to permit  
352 additional inhibitor analysis if needed. For further details please refer to chapter 5.3.

### 353 Viral safety

354 Compliance with CHMP recommendations with regard to viral safety (see chapter 5.2) is necessary and  
355 is verified by information supplied in Module 3 of the dossier.

356 A pre-treatment serum sample from each patient included in the clinical trials should be stored at  
357  $-70^{\circ}\text{C}$  for possible future testing.

### 358 **6.3. Clinical investigation in children <12 years**

359 Since children may respond differently compared to adults, a multicentre trial in children should be  
360 conducted. Due to the lower incidence of haemophilia B as compared to haemophilia A, the number of  
361 children to be enrolled should be at least 20, allocated to 2 age cohorts. A minimum of 10 patients  
362 should be PTPs (>150 ED) at the age of 6 - <12 years and at least 10 patients should be <6 years who  
363 have undergone >50 EDs with previous factor IX products. The clinical trial in children <12 years  
364 should not start before safety is proven for 50 EDs each of 10 patients who are included in the PTP trial  
365  $\geq 12$  years.

366 The clinical trial in children should begin with the investigation of pharmacokinetics (incremental  
367 recovery,  $t_{1/2}$ , AUC and clearance) in 10 patients of each age cohort. In order to allow for evaluation of  
368 a patient's individual response, existing pharmacokinetic information with patient's previous factor IX  
369 product (historical or recent recovery and half-life) should be available prior to first administration of  
370 the new factor IX product. With regard to patient compliance, PK sampling time points can be limited  
371 to measurements prior to infusion (baseline) and 1 hour, 10 hours, 24 hours and 48 hours after  
372 infusion. Depending on the type of factor IX product (e.g. prolonged half-life) sampling time points  
373 should be adjusted to cover the main parts of the activity time profile and to ensure that up to 5 half-  
374 lives are captured. It is anticipated that some deviation from the recommendation may occur in clinical  
375 practice; therefore, it is very important to record the exact time post-infusion at which the actual  
376 samples were collected and to use these values in the analysis. Preferably, the testing should be  
377 conducted in a central laboratory to decrease variability in test results.

378 Factor IX consumption (dose/kg for prophylaxis and therapy (on demand)) should be monitored as well  
379 as development of inhibitors in all the children participating in the study. Inhibitor testing should be  
380 performed following the same testing schedule as set out in Annex III and if there is any suspicion of  
381 inhibitor (see also chapter 5.3). In accordance with the requirements for the  $\geq 12$  years pre-  
382 authorisation PTP trial, the study in children should continue until the patients have received a  
383 minimum of 50 EDs to the investigational product. For all patients who develop inhibitors, a full clinical  
384 report should be provided including clinical relevance, the cumulative incidence and the number of EDs  
385 in relation to development of inhibitors. The titre of the inhibitor should be reported in Bethesda Units

386 using the modified Nijmegen assay. Plasma samples from patients who are suspected or confirmed to  
387 have inhibitors should be stored for possible future testing.

388 Within the application for marketing authorisation, pharmacokinetic data (incremental recovery,  $t_{1/2}$ ,  
389 AUC and clearance) as well as the completed efficacy and safety trial in 20 children (0 to <12y)  
390 followed for 50 EDs should be submitted.

391 For the post-marketing investigation, PTPs (>150 EDs) regardless of their age can be included  
392 provided that the pre-authorisation study in children <12 years is finished.

#### 393 **6.4. Clinical investigation in PUPs**

394 Previously untreated patients (PUPs) are defined as those patients who have never been treated with  
395 clotting factor products (except previous exposure to blood components). The concurrent development  
396 of many therapeutic products for haemophilia treatment decreases the availability of previously  
397 untreated patients for CTs, suggesting that informative studies performed in a meaningful number of  
398 PUPs will not be feasible in a timely manner. Therefore, formal PUP studies are not required; however,  
399 every PUP should be closely monitored with regards to treatment performance and inhibitor  
400 development through a well-defined and well-managed disease Registry. See chapter 8. Risk  
401 Management Plan.

#### 402 **6.5. Post-marketing investigation**

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

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

418 The number of patients typically needed in a post-marketing study with a factor IX product to cover  
419 especially immunogenicity aspects (besides general efficacy and safety) is 50. In case of plasma-  
420 derived factor IX products (e.g. manufactured by known methods, for national approval only) a smaller  
421 number of patients could be enrolled but justification should be provided. Study participants should be  
422 PTPs (>150EDs), and could be recruited regardless of their age, however, aiming for a balanced age  
423 distribution. In general, all patients from pre-authorisation clinical trials could be enrolled in post-  
424 marketing investigations.

425 The post-marketing investigation protocol will be approved at marketing authorisation as part of the  
426 risk management plan. A separate progress study report should be provided to the relevant Competent  
427 Authority(ies) 2 years after marketing authorisation to allow for evaluation of recruitment status,

428 progress and the adherence to timelines. The post-marketing investigation should be completed within  
429 4 years.

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

## 431 **7. Change in the manufacturing process**

432 Changes in the manufacturing process may lead to significant changes in the product and may thereby  
433 alter the structure of the coagulation factor and its activity. The effects of changes in the  
434 manufacturing process (e.g. viral inactivation steps or purification procedures) on the biological  
435 characteristics and activity of the product should be investigated. If significant impact on the activity of  
436 the coagulation factor cannot be excluded, data on pharmacokinetics, efficacy and safety should also  
437 be provided with the application. These data should be generated by following the comparability  
438 exercise (see ICH Q5E Note for Guidance on Biotechnological/Biological Products Subject to Changes in  
439 their Manufacturing Process (CPMP/ICH/5721/03) and Guideline on comparability of biotechnology-  
440 derived medicinal products after a change in the manufacturing process non-clinical and clinical issues  
441 (EMA/CHMP/BMWP/101695/2006)).

### 442 **7.1. General aspects on clinical trials**

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

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

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

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

### 458 **7.2. Efficacy**

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

465 A comparative pharmacokinetic trial with the "pre-change" product versus the "post-change" product  
466 should be performed in at least 12 PTPs suffering from haemophilia B (factor IX  $\leq 2\%$ ). The study  
467 should record incremental recovery, *in-vivo* half-life, area under the curve (AUC), and clearance in

468 patients without inhibitors who are not actively bleeding. Patients should be at least 12 years of age  
469 and should not have received an infusion of any factor IX product for at least 4 days. Samples should  
470 be taken before injection of 50-75 IU/kg of the factor IX product (baseline), 10-15 minutes (times  
471 refer to the interval after the completion of the infusion) and at 30 minutes, and 1 hour. Additional  
472 time points to include 3, 6, 9, 24, 48, and 60 hours post-infusion; a 72 hour sample is optional  
473 provided the patient was given at least 75 IU/kg. Depending on the type of factor IX product (e.g.  
474 prolonged half-life) further sampling time points could be necessary. A minimum of 3 different lots of  
475 the "post-change" product should be employed in the trial. Incremental recovery is determined as the  
476 peak level recorded 30 minutes after infusion and reported as [IU/ml]/[IU/kg].

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

479 Patients in the pharmacokinetic trial should continue treatment with the "post-change" product for  
480 6 months, and should be re-tested for the same pharmacokinetic parameters after 3-6 months using  
481 the same dose as in the first investigation.

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

## 485 **8. Risk management plan**

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

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

### 496 Inhibitor formation

497 The most serious complication of replacement therapy is the development of inhibitors although  
498 inhibitor occurrence in haemophilia B is less common than in haemophilia A. A comprehensive analysis  
499 of reported *de novo* and recurrent inhibitors should be provided as a cumulative report in RMP Annex  
500 VII, including:

- 501 • Source of inhibitor reports (e.g. clinical trial/post-authorisation investigation/spontaneous reports)
- 502 • Low and high titre, intermittent inhibitor.  
503 (Every positive laboratory test should be retested in a central laboratory with a second separately  
504 drawn sample from the same patient before a diagnosis of an inhibitor can be made. Samples  
505 should be stored for possible future testing.)

- 506 • Type 1 and 2 inhibitors

507 Classification of risk to develop factor IX inhibitor:

- 508 – Haemophilia severity
- 509 – Status of treatment (i.e. PUP/PTP)
- 510 – Cumulative exposure to factor IX products (total ED and ED on product)
- 511 – Type of gene mutation
- 512 – Age at first treatment
- 513 – Intensity of treatment
- 514 • Inhibitor incidence should be expressed as point estimate and 95 % CI.
- 515 • Special populations:
  - 516 – Patients who underwent surgery and subsequently develop inhibitors
  - 517 – Any specific risk (e.g. inhibitor development, lack of effect) induced in switching to the product
  - 518 from another factor IX product should be discussed separately. This is in particular relevant for
  - 519 products with a significant change in the manufacturing process. The switch from pre-change
  - 520 to post-change product should be investigated carefully.

#### 521 Lack of drug effect

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

#### 525 Hypersensitivity/anaphylactic reactions

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

#### 532 Thrombogenicity

533 Thrombotic events need to be monitored and reported.

#### 534 Measurement of plasma factor IX levels significantly affected by the assay used for clinical monitoring

535 Where there can be discrepant assay results depending on the assay used for clinical monitoring (see  
536 6.1.1), some information will be included in the product information but other approaches may also be  
537 needed including educational material for training of clinical laboratories. The Risk Management Plan is  
538 an appropriate place to address the risk of discrepant monitoring of plasma levels and the measures to  
539 avoid this.

#### 540 Registries

541 In order to complement information derived from clinical studies in PTPs required for marketing  
542 authorisation, every patient suffering from haemophilia, both PUPs and PTPs should be encouraged to  
543 enrol in disease specific registries. For novel products, e.g. those developed for their long-acting  
544 properties, it is crucial to identify and mitigate new safety issues that might emerge once a product is  
545 on the market.

546 Since a variety of haemophilia registries exist on national and international level a core parameter set  
547 is essential allowing for potential data merging and analysis and is proposed thereafter.

548 Core Data set:

549 **Administrative information**

- 550 • Registry
- 551 • Center

552

553 **Demographic information**

- 554 • Patient identifier
- 555 • Date of birth
- 556 • Gender

557 **Anamnestic information**

- 558 • Type of haemophilia
- 559 • Severity of haemophilia (% Factor activity)
- 560 • Date of diagnosis of haemophilia
- 561 • Family history of haemophilia/inhibitor (yes/no)
- 562 • Risk factors (e.g. FIX gene mutation)

563 **Haemophilia treatment information (each treatment)**

- 564 • Date of treatment
- 565 • Weight
- 566 • Product
- 567 • Treatment regimen/modality (on demand/prophylaxis)
- 568 • Dose
- 569 • Treatment reason (e.g. surgery, trauma, pain)

570 Bleeding (yes/no), if yes

- 571 ○ Reason
- 572 ○ Location
- 573 ○ Severity
- 574 ○ Follow up treatment

575 **Inhibitor information (each measurement)**

- 576 • Date of measurement
- 577 • Number of Exposure days



- 578 • Titer (BU/ml)
- 579 • Assay description (e.g. Nijmegen, Bethesda, ELISA)

580 **Relevant information on concomitant events (e.g. infections, allergic reactions)**

- 581 • Date of event onset
- 582 • Event description
- 583 • Date event resolved

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

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

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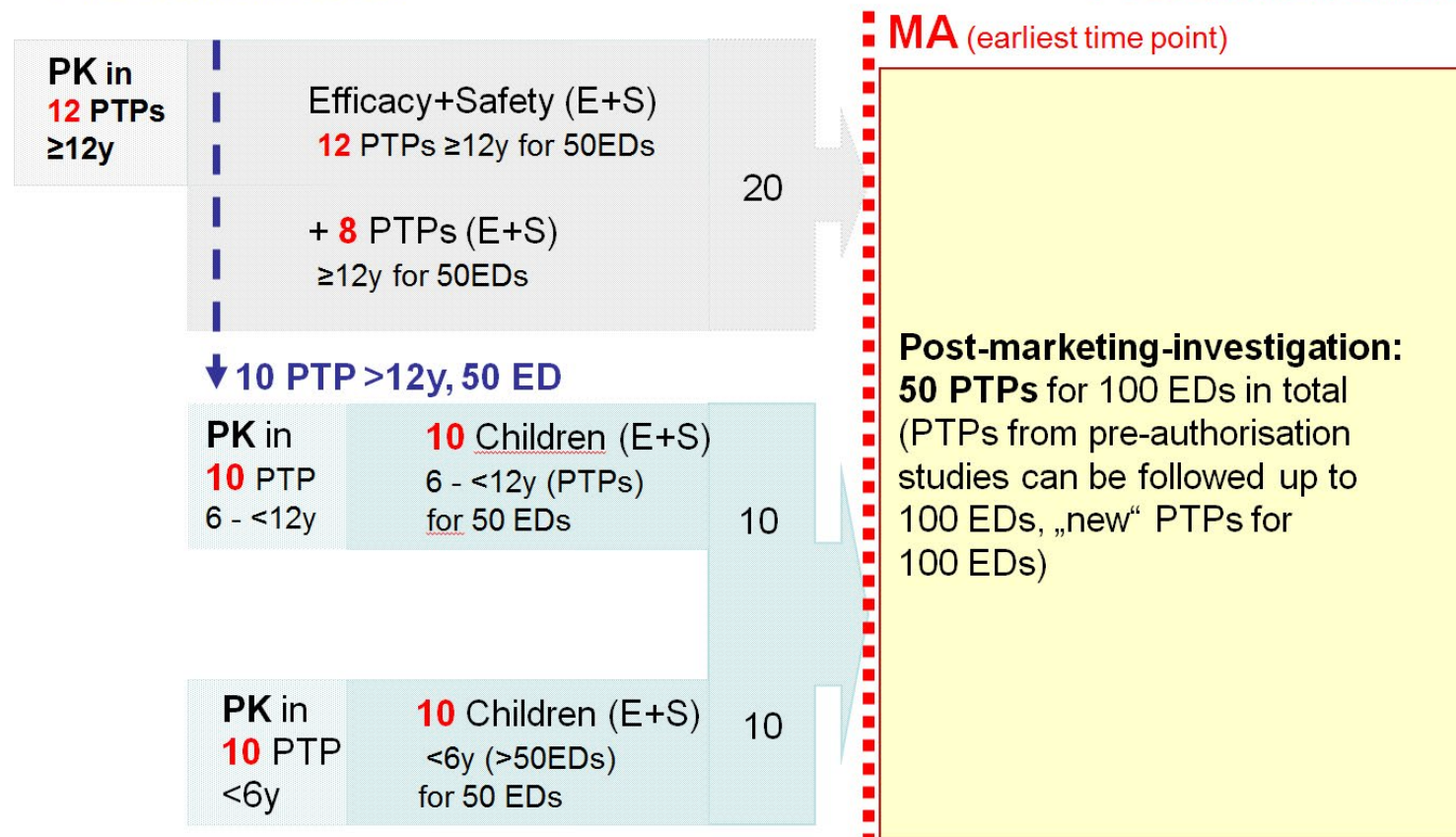
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## Annex I – Overview on clinical trial concept

### Pre-authorisation

### Post-authorisation



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

Trial, subject	Investigation	Parameters
<b>PTP ≥12y study – pre-authorisation</b>		
12 haemophilia B patients (PTP ≥12 years; factor IX ≤2%) without inhibitors and not actively bleeding	Pharmacokinetics <sup>2</sup>	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.
<b>Children &lt; 12y study – pre-authorisation</b> (to be started after results of 50 ED in 10 PTPs (≥12 years) have become available.)		
10 haemophilia B patients (PTPs, <b>6 - &lt;12y</b> ; 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.
10 haemophilia B patients (>50 EDs, < <b>6y</b> ; factor IX ≤2%) without inhibitors and not actively bleeding		
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

<sup>2</sup> 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
		any suspicion of inhibitor development. Continue until a minimum of 50 exposure days.
	Safety	Adverse events. Thrombogenicity.
<b>Post-marketing investigation</b>		
<b>50 PTPs</b> 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:  $\leq 2\%$  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  $> 200/\mu\text{l}$ , HIV negative or having a viral load  $< 200$  particles/ $\mu\text{l}$   $\sim 400000$  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/ $\mu\text{l}$   $\sim 400000$  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 <sup>†</sup>	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

<sup>†</sup>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 t<sub>1/2</sub> 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.