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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)

10
11 Comments should be provided using this [template](#). The completed comments form should be sent to
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12 Guideline on the clinical investigation of recombinant and
13 human plasma-derived factor IX products

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42 **GLOSSARY**

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

66 **Executive summary**

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

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

96 **1. Introduction (background)**

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

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

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

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

107 These data are required for:

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

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

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

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

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

123 **2. Scope**

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

127 **3. Legal basis**

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

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

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

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

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

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

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

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

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

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

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

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

149 GVP module V – Risk Management Systems

150 **4. Efficacy: General aspects**

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

161 **5. Safety: General aspects**

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

166 **5.1. Adverse events**

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

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

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

176 **5.2. Safety with respect to viruses and other transmissible agents**

177 Recombinant products

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

183 Plasma-derived products

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

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

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

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

202 **5.3. Immunogenicity**

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

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

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

219 **5.4. Thrombogenicity**

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

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

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

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

232 **6.1. General aspects on clinical trials**

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

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

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

256 **6.1.1. Potency measurement**

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

^{*} 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

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

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

274 **6.2. Efficacy in PTPs ≥ 12 years**

275 Choice of patients

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

284 Pharmacokinetics

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

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

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

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

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

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

313 Efficacy including surgery

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

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

327 Continuous infusion

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

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

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

334 (if necessary plus a corresponding safety margin)

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

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

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

343 Immunogenicity testing

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

354 Viral safety

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

357 A pre-treatment serum sample from each patient included in the clinical trials should be stored at
358 -70°C for possible future testing.

359 **6.3. Clinical investigation in children <12 years**

360 Since children may respond differently compared to adults, a multicentre trial in children should be
361 conducted. Due to the lower incidence of haemophilia B as compared to haemophilia A, the number of
362 children to be enrolled should be at least 20, allocated to 2 age cohorts. A minimum of 10 patients
363 should be PTPs (>150 ED) at the age of 6 - <12 years and at least 10 patients should be <6 years who
364 have undergone >50 EDs with previous factor IX products. The clinical trial in children <12 years
365 should not start before safety is proven for 50 EDs each of 10 patients who are included in the PTP trial
366 ≥ 12 years.

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

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

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

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

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

394 **6.4. Clinical investigation in PUPs**

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

403 **6.5. Post-marketing investigation**

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

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

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

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

429 progress and the adherence to timelines. The post-marketing investigation should be completed within
430 4 years.

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

432 **7. Change in the manufacturing process**

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

443 **7.1. General aspects on clinical trials**

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

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

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

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

459 **7.2. Efficacy**

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

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

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

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

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

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

486 **8. Risk management plan**

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

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

497 Inhibitor formation

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

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

- 507 • Type 1 and 2 inhibitors

508 Classification of risk to develop factor IX inhibitor:

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

522 Lack of drug effect

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

526 Hypersensitivity/anaphylactic reactions

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

533 Thrombogenicity

534 Thrombotic events need to be monitored and reported.

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

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

541 Registries

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

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

549 Core Data set:

550 **Administrative information**

- 551 • Registry
- 552 • Center

553

554 **Demographic information**

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

558 **Anamnestic information**

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

564 **Haemophilia treatment information (each treatment)**

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

571 Bleeding (yes/no), if yes

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

576 **Inhibitor information (each measurement)**

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

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

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

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

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

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

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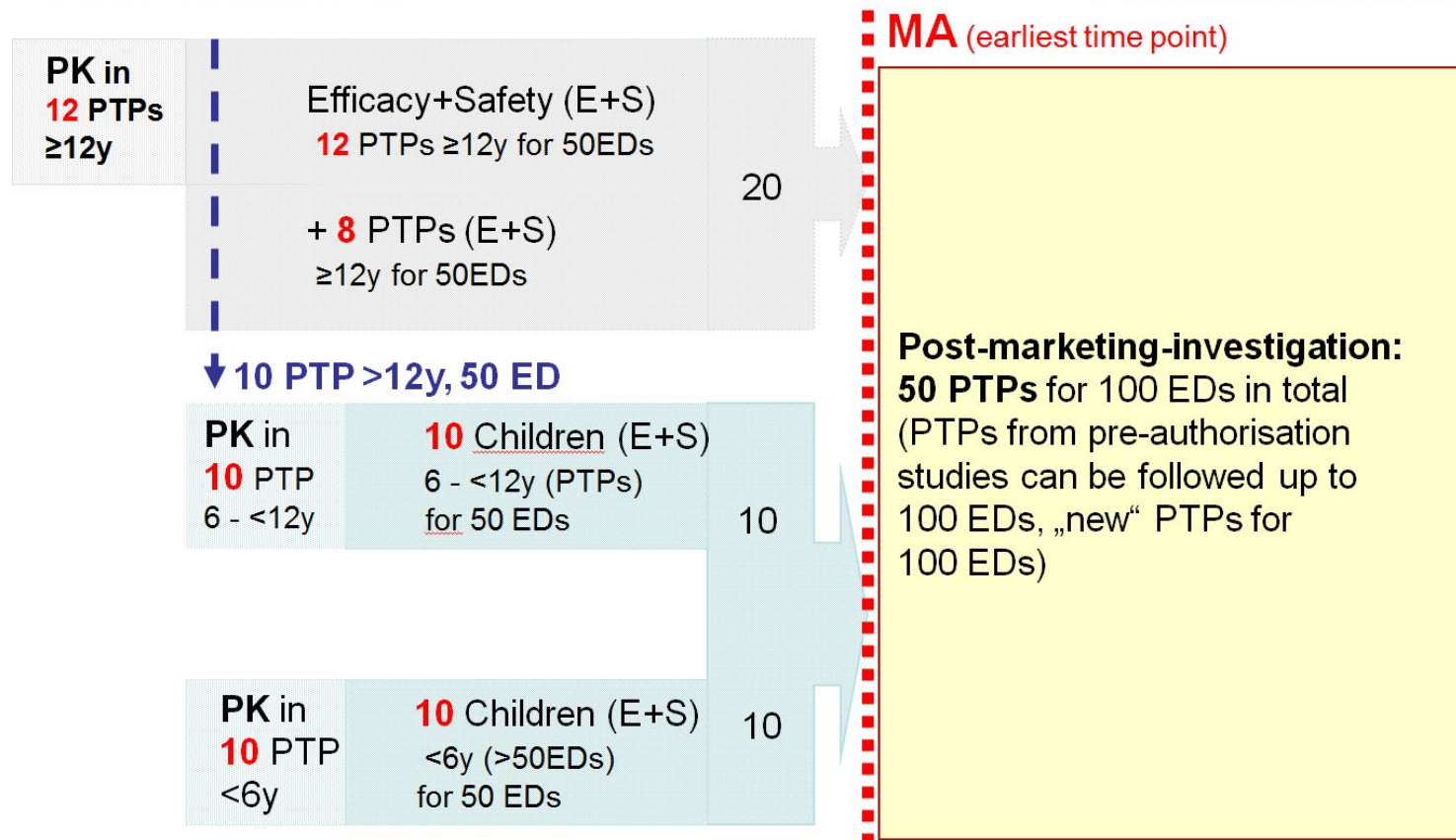
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Annex I – Overview on clinical trial concept

Pre-authorisation

Post-authorisation



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

Trial, subject	Investigation	Parameters
PTP ≥12y study – pre-authorisation		
12 haemophilia B patients (PTP ≥12 years; factor IX ≤2%) without inhibitors and not actively bleeding	Pharmacokinetics ²	Incremental recovery, half-life, AUC, clearance. Patients should be re-tested after 3-6 months (including factor IX inhibitor assay).
	Safety	Blood pressure, heart rate, temperature, respiratory rate and adverse events. Thrombogenicity.
5 haemophilia B patients (PTP ≥12 years; factor IX ≤2%) undergoing at least 10 surgical procedures	Clinical efficacy	Efficacy of haemostasis, loss of blood and requirement for transfusion. Factor IX consumption.
	Safety	Adverse events. Thrombogenicity.
Efficacy and safety in 20 PTPs (≥12 years; factor IX ≤2% and CD4>200/μl)	Clinical efficacy	Factor IX consumption, physician's assessment of response in treatment of major bleeds.
	Immunogenicity	Inhibitor titre in Bethesda Units immediately before first exposure, ED10-15, ED50-75 and if there is any suspicion of inhibitor development, continue for a minimum of 50 exposure days.
	Safety	Adverse events. Thrombogenicity.
Children < 12y study – pre-authorisation (to be started after results of 50 ED in 10 PTPs (≥12 years) have become available.)		
10 haemophilia B patients (PTPs, 6 - <12y ; factor IX ≤2%) without inhibitors and not actively bleeding	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, <6y ; 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

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

Trial, subject	Investigation	Parameters
		any suspicion of inhibitor development. Continue until a minimum of 50 exposure days.
	Safety	Adverse events. Thrombogenicity.
Post-marketing investigation		
50 PTPs for 100 EDs in total (PTPs from pre-authorisation studies can be followed up to 100 EDs, “new” PTPs for 100 EDs)	Clinical efficacy Immunogenicity Safety	Protocol should be provided according to Annex III.

Annex III – Post-marketing investigation

Inclusion criteria

- Diagnosis: haemophilia B
- Factor IX activity: $\leq 2\%$ 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/ μl ~ 400000 copies/ml

Documentation of Patient's characteristics

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

Patient enrolment

- At least 50 patients per post-marketing investigation
- Follow-up of each patient must be at least 100 ED
- Progress on recruitment has to be reported on a regular basis (will be set out before approval of procedure)
- A separate progress study report should be provided to the relevant Competent Authority(ies) 2 years after marketing authorisation to allow for evaluation of recruitment status, progress and the adherence to timelines.
- The post-marketing investigation should be completed within 4 years.

Study procedures

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

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

*after washout period (see Explanatory Note); storage of back up blood sample is recommended

#new patients = not recruited for pre-authorisation studies

[†]baseline inhibitor testing prior to first infusion of test product

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

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

Explanatory Note

Inhibitor tests should be performed when the plasma factor IX level has reached a pre-substitution nadir (documentation for the last infusion should be provided). Inhibitor questionnaires/report forms should be used. In the case that patients are treated on demand, an inhibitor can be missed when the patients did not receive treatment for > 2 weeks. According to the t_{1/2} of immunoglobulins, the inhibitor will drop gradually when treatment has been stopped. In case of a positive inhibitor test, also PK / recovery tests are necessary to confirm inhibitory activity.

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