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3 Committee for Medicinal Products for Human Use (CHMP)

4 **Guideline on the clinical investigation of human normal**
5 **immunoglobulin for intravenous administration (IVIg)**
6 **Draft**

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7
8 This guideline replaces Guideline on the Clinical Investigation of Human Normal Immunoglobulin for
9 Intravenous Administration (IVIg) (CPMP/BPWG/388/95 rev.1).

10 **Important note**

11 Draft guideline CPMP/BPWG/388/95 rev.2 was released for public consultation in August 2009. The
12 purpose of this second public consultation is to specifically seek comments on the ITP section (7.3.3)
13 where there are significant changes in the recommendations from the previous draft revision in order
14 to encompass the recommendations by Rodeghiero F. *et al.* Standardization of terminology, definitions
15 and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an
16 international working group. *Blood*. 2009;113:2386-2393.



17 Please do not provide comments on other parts of the guideline that were already provided during the
18 2009 consultation. These are being taken into account in this on-going revision process and an
19 overview of all comments received with outcomes will be published at the time of finalisation of the
20 guideline.

Comments should be provided using this [template](#). The completed comments form should be sent to ludmila.svobodova@ema.europa.eu.

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Keywords	<i>IVIg, human normal immunoglobulin, primary immunodeficiency syndromes, hypogammaglobulinaemia, primary immune thrombocytopenia (= idiopathic thrombocytopenic purpura) (ITP), Guillain Barré syndrome, Kawasaki disease, multifocal motor neuropathy (MMN), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), myasthenia gravis exacerbations.</i>
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23 Guideline on the clinical investigation of human normal
24 immunoglobulin for intravenous administration (IVIg)

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61 **Executive summary**

62 This Guideline describes the information to be documented when an application is made for a
63 marketing authorisation for a human normal immunoglobulin for intravenous use (IVIg). The guidance
64 covers biological data, clinical trials and patient follow-up. Quality aspects are outside the scope of this
65 guideline.

66 Guidance is also provided for authorised products where a significant change in the manufacturing
67 process has been made.

68 **1. Introduction (background)**

69 The purpose of this Guideline is to provide applicants and regulators with harmonised guidance for
70 applications for marketing authorisation for IVIg.

71 **2. Scope**

72 This guideline describes the information to be documented when an application for a marketing
73 authorisation for IVIg is made, including biological data, pharmacokinetics, clinical trials and patient
74 follow-up.

75 These data are required for:

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

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

82 This Guideline covers normal human immunoglobulin for intravenous administration defined by the
83 European Pharmacopoeia monograph 0918. The Guideline does not relate to fragmented or chemically
84 modified products.

85 Quality aspects are also outside the scope of this guideline.

86 **3. Legal basis**

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

89 **4. Background**

90 The first use of polyvalent intravenous immunoglobulin preparations was as replacement therapy in
91 humoral immunodeficiency situations. As human normal immunoglobulin for intravenous
92 administration (IVIg) is prepared from plasma collected from a high number of healthy blood donors,
93 the spectrum of antibody specificity expressed by the IgG is large. Among the antibody specificity
94 spectrum, IVIg recognises a large number of bacterial, viral and other infectious agent antigens, and
95 also a large number of self antigens. Besides the therapeutic effect in replacement, IVIg has thus also
96 been used for its immunomodulatory activity.

97 Indications of IVIg are described in two main sections referred to as “replacement therapy” and
98 “immunomodulatory effect”. While the immunodeficient conditions covered by the replacement effect
99 of IVIg are quite well-defined, the immunomodulatory effect of IVIg has been demonstrated in a
100 limited number of diseases only. Lists of such auto-immune-related diseases have been established by
101 various national and international bodies and are constantly updated.

102 Timeline of first revision was as follows:

- | | | |
|-----|---|---------------|
| 103 | • Discussion in Blood Products Working Group | June 1999 |
| 104 | • Release for consultation | June 1999 |
| 105 | • Deadline for comments | December 1999 |
| 106 | • Discussion in Blood Products Working Group | May 2000 |
| 107 | • Final adoption by Committee for Medicinal Products for Human Use (CHMP) | December 2000 |

108 **5. Efficacy**

109 Biological data and clinical evidence of efficacy and safety in primary/secondary humoral
110 immunodeficiencies and ITP are the key elements required for the licensing of IVIg in the following
111 claimed indications:

112 Replacement therapy in:

- 113 • Primary immunodeficiency syndromes with impaired antibody production.
- 114 • Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic
115 leukaemia (CLL), in whom prophylactic antibiotics have failed.
- 116 • Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma
117 (MM) patients who have failed to respond to pneumococcal immunisation.
- 118 • Children and adolescents with congenital AIDS and recurrent bacterial infections.
- 119 • Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation
120 (HSCT).

121 Immunomodulatory effect in:

- 122 • Primary immune thrombocytopenia* (ITP) in children or adults at high risk of bleeding or prior to
123 surgery to correct the platelet count
- 124 • Guillain Barré Syndrome (GBS)
- 125 • Kawasaki disease

126 The listed indications are considered as “established” for IVIg and this guideline outlines the general
127 principles for design of clinical trials.

128 For other auto-immune disorders (in particular multifocal motor neuropathy (MMN), chronic
129 inflammatory demyelinating polyradiculoneuropathy (CIDP), myasthenia gravis exacerbations)
130 confirmatory data are required, see 7.3.5.

131 In other indications, relevant clinical data are required, see 7.3.6.

* The term idiopathic thrombocytopenic purpura has been exchanged for primary immune thrombocytopenia according to the recommendations of an International Working Group (IWG) in “Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children”¹. The acronym will remain the same.

132 **6. Safety**

133 **6.1. Adverse events**

134 All adverse events in clinical studies must be recorded and analysed with regard to causality,
135 seriousness, outcome and expectedness (see 7.4.1.). A detailed protocol of the studies specifying the
136 methods for collection, intervals for collection of the data and duration of follow up is requested.

137 Safety data from trials in indications not claimed in the application can be used as supportive data.

138 **6.2. Safety with respect to transmissible agents**

139 **6.2.1. Viral Safety**

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

144 The above-mentioned procedures are now considered to be highly effective and demonstrative of the
145 viral safety of the product with respect to enveloped viruses.

146 These procedures may be of limited value against non-enveloped viruses, such as hepatitis A virus and
147 parvovirus B19 and as the safety of the products with respect to non-enveloped viruses cannot
148 currently be adequately evaluated in clinical studies, the antibody content against these viruses should
149 be examined.

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

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

157 **6.2.2. Other transmissible agents**

158 Similar principles to those outlined in 6.2.1 apply for safety with regard to other transmissible agents
159 including TSE and other emerging pathogens. Manufacturers should follow the respective guidance
160 documents and position statements. Information can be found in the section "Guidelines on Plasma-
161 derived Medicinal Products" on the EMEA website: (<http://www.emea.europa.eu/htms/human/humanguidelines/biologicals.htm>).

163 **6.3. Other safety issues**

164 The effect of passive transmission of haemagglutinins (anti-A/anti-B), and anti-D should be evaluated
165 in patients receiving high doses of IVIg.

166 **7. Product for which and application for a marketing**
167 **authorisation is to be submitted: "New products"**

168 Biological and pharmacokinetic data are the key elements to evaluate activity and safety of IVIg
169 preparations.

170 **7.1. Biological data**

171 Adequate documentation with regard to batch to batch consistency is provided in Module 3 of the
172 dossier and should follow the Ph. Eur. Monograph 0918 requirements.

173 However, specific data are needed to support the pharmacodynamic and therapeutic activities as well
174 as the safety profile of the IVIg preparation. The data should include the following parameters and be
175 summarised along with the cross-reference to Module 3 (wherever applicable), in Module 5 of the
176 dossier.

177 *i) Biological characteristics*

178 General

179 • Molecular size distribution: quantification of monomers, dimers, fragments, polymers and
180 aggregates.

181 • Impurities (proteins -IgA, IgM, IgE, - other).

182 For pharmacodynamic and therapeutic activity

183 • Distribution of IgG subclasses

184 • Content of clinically relevant antibodies to:

185 – bacteria, such as: *C. diphtheriae*; *H. influenzae* type B; *S. pneumoniae*, *S. pyogenes*.

186 – viruses, such as: hepatitis A and B viruses; cytomegalovirus; varicella-zoster virus; rubella,
187 measles virus; parvovirus B19; poliomyelitis virus type I

188 Other

189 • Anti-complementary activity

190 • Anti-A and anti-B haemagglutinins

191 • Haemolysins (usually anti-A and anti-B)

192 • Anti-D antibodies

193 • Prekallikrein activator.

194 *ii) Biological activity*

195 • *In vivo* and/or *in vitro* quantification of neutralising antibodies (depending on the claimed
196 neutralising activities)

197 • Fab and Fc functions (functional integrity): antigen-driven complement fixation, opsonisation,
198 phagocytosis, antibody-dependent cell-mediated cytotoxicity (ADCC).

199 Immunomodulatory and anti-inflammatory activities for auto-immune diseases, depending on the
200 claimed indications and the relevance of *in vitro* and/or *in vivo* models such as:

201 • Ability to inhibit auto-antibody activity *in vitro*

- 202 • Experimental autoimmune models.

203 **7.2. Pharmacokinetics**

204 Pharmacokinetic (PK) data are essential to support the pharmacological activity and efficacy of the
205 product, and may differentiate one product from another. Therefore, they must be provided in each
206 application dossier (see PK study chart).

207 PK parameters

- 208 1. IgG trough levels should be studied in 40 patients with primary immunodeficiency syndromes
209 (PID), whereby 20 of these should be children or adolescents with an age distribution
210 representative of this patient population. The IgG trough levels of the investigational product
211 should be assessed prior to each infusion over a period of 6 months, starting after 5-6
212 administrations of the product (6.5 times the expected half-life). The IgG trough levels obtained
213 should be compared to either the trough levels of the former product (in previously treated
214 patients) or to literature data (in patients naïve to IVIg treatment), whereby predefined
215 comparability limits should be justified by the applicant.
- 216 2. Other PK parameters including plasma concentration-time curve, half-life, area under the curve,
217 volume of distribution, C_{max}, T_{max}, and elimination rate constant(s) should be measured in 20
218 adult PID patients assessed by repeated blood sampling after approximately 5-6 administrations of
219 the product until immediately before the next infusion. The other PK parameters obtained should
220 be discussed by the applicant in the light of the literature data.

221 PK population

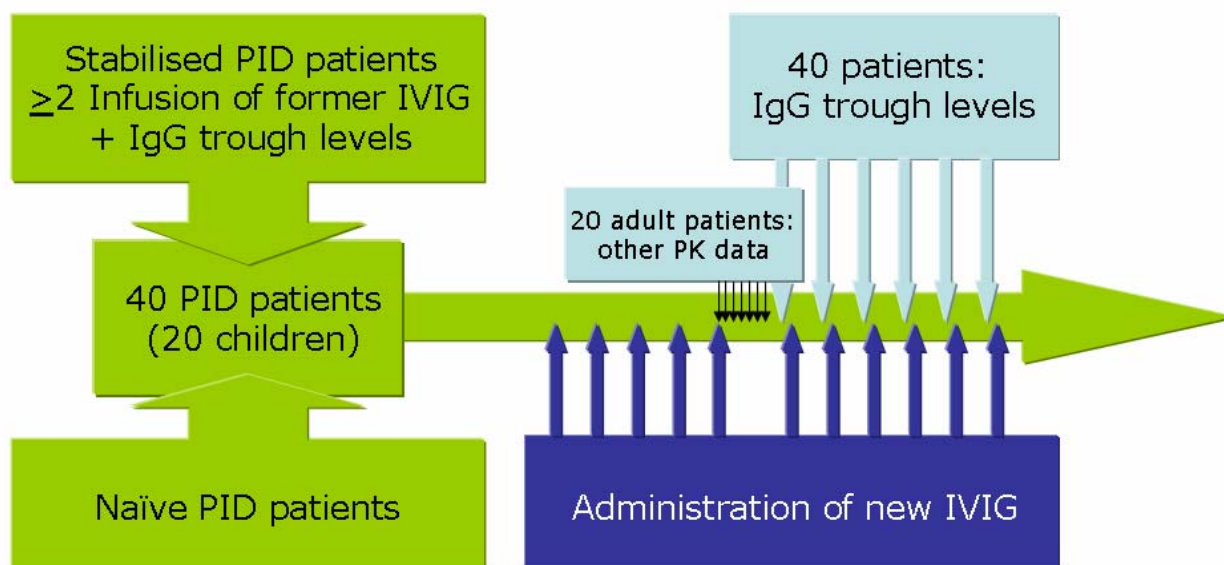
222 Pharmacokinetic data set can be derived from patients with primary immunodeficiency syndromes
223 (PID) who are either in group A) already stabilised on IVIG treatment or in group B) naïve to IVIG
224 treatment or the set can contain both patient groups.

225 A) Patients already stabilised on IVIg treatment

226 In patients already stabilised with another IVIg preparation, trough levels and treatment intervals
227 should be documented for at least two previous infusions, prior to the introduction of the new IVIg
228 preparation. After a period of approximately 5-6 administrations of the product (3-5 estimated half-
229 lives) with the new IVIg product, trough levels and treatment intervals should be measured.

230 B) Patients naïve to IVIg treatment

231 In patients naïve to IVIg the pharmacokinetic profile should be assessed when steady state (T_{ss}) is
232 reached.



234

235 **7.3. Efficacy**

236 IVIg is used as replacement therapy for the treatment of primary and secondary immunodeficiencies.

237 **7.3.1. Replacement therapy in primary immunodeficiency syndromes**

238 Efficacy should be proven in an open clinical trial of one year duration in primary immunodeficiency
 239 syndromes. The patients selection should take into account statistical considerations (see below).

240 At least 40 patients should be included; approximately half of these patients should be children and
 241 adolescents of various age categories. The patients should be followed over 12 months to avoid a
 242 seasonal bias (due to a greater rate of infections in the winter months).

243 The recommended primary endpoint is the number of serious bacterial infections (less than 1.0
 244 infection/subject/year). The protocol should prospectively provide specific diagnostic criteria for each
 245 type of serious infection to be included in the primary efficacy analysis. Serious bacterial infections
 246 include:

- 247 • bacteraemia or sepsis,
- 248 • bacterial meningitis,
- 249 • osteomyelitis / septic arthritis,
- 250 • bacterial pneumonia,
- 251 • visceral abscess.

252 Secondary endpoints are IgG trough levels (see PK section), all other infections, antibiotic treatment,
 253 days lost from school/work, hospitalisations and fever episodes.

254 Statistical considerations

255 The number of subjects to be included into the study might exceed 40 patients as the study should
 256 provide at least 80% power to reject the null-hypothesis of a serious infection rate greater or equal 1
 257 by means of a one-sided test and a Type I error of 0.01.

258 The secondary endpoints should be prospectively defined and their statistical analyses provided in the
259 study protocol.

260 The efficacy results would apply to all types of primary immunodeficiency syndromes due to deficiency
261 of functional IgG.

262 **7.3.2. Replacement therapy in other immunodeficiency syndromes**

263 1. Hypogammaglobulinaemia and recurrent bacterial infections in patients with CLL, in whom
264 prophylactic antibiotics have failed.

265 2. Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase MM patients who
266 have failed to respond to pneumococcal immunisation.

267 3. Children and adolescents with congenital AIDS and recurrent bacterial infections.

268 4. Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation
269 (HSCT)

270 The above indications would be granted as long as efficacy has been proven in primary
271 immunodeficiency syndromes (see 7.3.1). Standard doses are 0.2-0.4 g/kg every three to four weeks.
272 If other dosage regimens are requested, they should be supported by clinical data.

273 **7.3.3. ITP**

274 IVIg is used for the treatment of ITP in children, adolescents or adults at high risk of bleeding or prior
275 to surgery to correct the platelet count.

276 There are no data to support the equivalence of different IVIg preparations, especially with regard to
277 immunomodulatory activities. Thus a clinical efficacy study is required to establish the product efficacy
278 in this indication.

279 Efficacy study

280 An open, study with the investigational IVIg should be performed in 30 chronic (> 12 months duration)
281 adult ITP patients with a baseline platelet count of $<30 \times 10^9/l$. The results should be compared to data
282 from the literature. Standard doses should be studied (0.8 - 1 g/kg on day one, which may be
283 repeated once, or 0.4 g/kg/day for 2-5 days). If other dosage regimens are requested, they should be
284 supported by clinical data.

285 Baseline data on splenectomy and co-medication (especially affecting bleeding or platelets) should be
286 provided. Patients included in the study may have refractory ITP i.e. the failure to achieve at least a
287 response or loss of response after splenectomy and the need of treatment(s) to minimize the risk of
288 clinically significant bleeding. In clinical practice refractory patients may need on demand IVIG to
289 temporarily increase the platelet count sufficiently to safely perform invasive procedures or in case of
290 major bleeding or trauma; the platelet count to be reached will depend on the nature of the invasive
291 procedure

292 Corticosteroids are permitted if the patient is either on long-term stable doses of corticosteroids or the
293 platelet count falls below $30 \times 10^9/l$ again, but should not to be given as a pre-treatment to alleviate
294 potential tolerability problems. Patients with increases in corticosteroid doses during the duration of
295 response period of the study should be regarded as treatment failures. Any concomitant medication
296 during the trial should be documented and possible confounding impact on the outcome of the trial
297 assessed.

298 Efficacy parameters:

299 Platelet counts should be confirmed on at least 2 separate occasions (at least 7 days apart when used
300 to define complete response (CR) and response (R) or 1 day apart when used to define no response
301 (NR) or loss of response.

- 302 • Number and % of patients with CR: platelet count $\geq 100 \times 10^9/L$ and absence of bleeding
- 303 • Number and % of patients with R: platelet count $\geq 30 \times 10^9/L$ and at least 2-fold increase the
304 baseline count and absence of bleeding
- 305 • Time to response: time from starting treatment to time of achievement of CR or R (Late responses
306 not attributable to the investigated treatment should not be defined as CR or R)
- 307 • Number and % of patients with NR: platelet count $< 30 \times 10^9/L$ or less than 2-fold increase of
308 baseline platelet count or bleeding
- 309 • Number and % of patients with loss of CR or R: platelet count below $100 \times 10^9/L$ or bleeding (from
310 CR) or below $30 \times 10^9/L$ or less than 2-fold increase of baseline platelet count or bleeding (from R)

311 Duration of response

- 312 • Measured from the achievement of CR or R to loss of CR or R

313 Statistical considerations

- 314 • Wherever possible platelet parameters should be provided as mean (+ standard deviation) and
315 median (+ minimum and maximum) values for each patient, as well as for summary data.

316 **7.3.4. Guillain Barré syndrome, Kawasaki disease**

317 In the absence of specific clinical trial data in these indications, the efficacy in primary
318 immunodeficiency syndromes and in ITP should be established.

319 Published literature in Guillain Barré syndrome and Kawasaki should be provided. The applicability of
320 these data, including the dosage regimen, to the IVIg should be justified in the expert report. If other
321 dosage regimens are requested, they should be supported by clinical data.

322 In Kawasaki disease, patients should receive concomitant treatment with acetylsalicylic acid.

323 **7.3.5. Other auto-immune disorders**

324 Published literature indicates a positive effect of IVIGs in some auto-immune disorders in particular
325 multifocal motor neuropathy (MMN), chronic inflammatory demyelinating polyradiculoneuropathy
326 (CIDP), and myasthenia gravis exacerbations[†]. For these indications the efficacy in primary
327 immunodeficiency syndromes and in ITP should be established. The applicant should also provide

- 328 • An analysis of the existing literature and,
- 329 • Confirmatory data with the applicant's IVIg (see also 'Guideline on Clinical Trials in Small
330 Populations', CHMP/EWP/83561/2005), This should include a justification for the
 - 331 – scope of the confirmatory dataset (sample size, dose, time frame, patient population),
 - 332 – choice of the neurological scale and clinically meaningful differences within the chosen scale

[†] The existing legislation provides various incentives for the development of new indications through orphan medicinal products, paediatric-use marketing authorisations, and an additional year of data exclusivity for a new indication of an existing product.

- 333 – comparator arm,/ or lack of comparator
- 334 – wash-out period of previous medication and/or stable co-medication
- 335 • The investigation of other auto-immune indications should be in accordance with the Paediatric
336 Regulation ([EC No 1901/2006](#))

337 **7.3.6. Other indications**

338 Other possible indications cannot be granted without relevant specific clinical data. Biological and
339 pharmacokinetic data alone are not sufficient to support clinical efficacy.

340 Controlled clinical trials comparing the IVIg preparation with placebo or with an established therapy are
341 thus required to substantiate marketing authorisation in other indications.

342 The investigation of other indications should be in accordance with the Paediatric Regulation.

343 **7.4. Safety**

344 Product safety is evaluated based on all pertinent safety findings. A comprehensive risk management
345 plan (RMP) has to be submitted as part of the dossier (see Guideline on 'risk management systems for
346 medicinal products for human use', EMEA/CHMP/96268/2005).

347 **7.4.1. Adverse events**

348 Comprehensive baseline data and patient histories are essential to compare the safety signals arising
349 from the studies. The safety signals should be compared with data and frequencies described in the
350 literature. Any deviation from known signals and rates should be discussed. Adverse events (AEs) and
351 serious adverse events (SAEs) from all subjects followed throughout the clinical studies should be
352 recorded and reported regardless of whether the AE is determined to be related to the product or not.
353 The reporting should be in accordance with the ICH Guidelines on "Structure and content of clinical
354 study report", CPMP/ICH/137/95 E3. Preferably the reporting should apply the terminology used in the
355 Medical Dictionary for Regulatory Activities (MedDRA).

356 Safety evaluation should include monitoring of short term tolerance (blood pressure, heart rate,
357 temperature, and monitoring of other adverse events) at repeated intervals following the infusion of
358 the new product. All AEs that begin during or within 72 hours after an infusion should be classified and
359 analysed as infusional AEs.

360 AEs should be evaluated with regard to the infusions rates. Renal function should be monitored,
361 particularly in patients at risk and in those receiving high doses of IVIg.

362 All safety data should include a separate evaluation of the safety dataset in children and adolescents.
363 This should be compared to the adult dataset and relevant discrepancies listed in the SPC.

364 Post-marketing safety data collection in children should be proposed in the risk management plan.

365 A separate safety evaluation of the excipients should be provided; which should encompass a summary
366 of the non-clinical and literature data.

367 **7.4.2. Safety with respect to transmissible agents**

368 Compliance with CHMP recommendations with regard to viral safety and other transmissible agents
369 under 6.1.2 above is necessary for all plasma-derived products and is verified by information supplied
370 in Module 3 of the dossier.

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

373 **7.4.3. Other safety issues**

374 The effect of passive transmission of haemagglutinins and haemolysins (anti-A/anti-B), and anti-D
375 should be evaluated in patients receiving high doses of IVIg, by searching for haemolysis and
376 performing a Direct Antiglobulin Test (DAT; direct Coomb's test) in the patient.

377 **7.5. Paediatrics regulation**

378 Where a paediatric investigation plan is required in order to comply with the Paediatric Regulation ([EC](#)
379 [No 1901/2006](#)), the applicant should provide a plan covering the recommendations described in this
380 guideline for the paediatric population.

381 **8. Change in the manufacturing process of authorised** 382 **products**

383 Changes in the manufacturing procedures may lead to significant changes in the product and may
384 thereby alter the structure of the immunoglobulin and/or its activity or the safety of the product.

385 If a significant impact on the activity of the immunoglobulin cannot be excluded, data on
386 pharmacokinetics in PID patients and efficacy and safety in ITP patients should also be provided with
387 the application.

388 **8.1. General aspects on clinical trials**

389 When a change is introduced to the manufacturing process of a given product, the marketing
390 authorisation holder will have to demonstrate that the "post-change" and the "pre-change" product are
391 comparable in terms of Quality, Safety and Efficacy (see ICH Q5E Guideline on "Comparability of
392 Biotechnological Products (CPMP/ICH/5721/03)). This will be a sequential process, beginning with
393 investigations of quality and supported, as necessary, by non-clinical and/or clinical studies.

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

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

400 If the biological and pharmacokinetics are significantly different from the parent preparation, then the
401 product should comply with the requirements for new product as defined in section 7.

402 **8.2. Biological data**

403 The effects of changes in the manufacturing process (e.g. viral inactivation steps, changes in pH,
404 changes of excipients, changes in dimer content or new purification procedures) on the biological
405 characteristics and activity of the product should be investigated.

406 Thus, it is important to include full data on antibody integrity and function in Module 3 and cross-refer
407 to this in Module 5 of the dossier as for new products.

408 **8.3. Pharmacokinetics**

409 Plasma concentration-time curve, half-life, area under the curve, volume of distribution, C_{max}, T_{max},
410 and elimination rate constant(s) should be measured in 20 adult PID patients assessed by repeated
411 blood sampling after approx. the 5-6 administrations of the product until immediately before the next
412 infusion. These PK parameters should be compared to data obtained with the predecessor product.

413 **8.4. Efficacy and safety**

414 For ITP, since the biological rationale for efficacy is not completely elucidated, a further clinical study is
415 required as outlined above in 7.3.3.

416 The remaining indications that were granted for the parent product (i.e. prior to the changes in the
417 manufacturing procedures) can be granted by reference to the literature, providing that efficacy has
418 been established in ITP for the changed product.

419 PID patients included in the limited PK study (8.2) and ITP patients should be evaluated for safety
420 according to the principles outlined in 7.4.

421 Requirements for viral safety and other transmissible agents are the same as for the parent product
422 (see 7.4.2).

423 **Definitions**

424 CIDP Chronic inflammatory demyelinating polyradiculoneuropathy

425 GBS Guillain Barré Syndrome

426 ITP Primary immune thrombocytopenia

427 MMN Multifocal motor neuropathy

428 **References**

429 ¹ Rodeghiero F. et al. Standardization of terminology, definitions and outcome criteria in immune
430 thrombocytopenic purpura of adults and children: report from an international working group. *Blood*.
431 2009; 113: 2386-2393