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Committee for Medicinal Products for Human Use

**GUIDELINE ON THE INVESTIGATION OF MEDICINAL PRODUCTS IN THE TERM AND
PRETERM NEONATE**

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¹ Last day of relevant Committee meeting

² Last day of the month concerned

³ If other WPs have been involved in discussions this needs to be specified

⁴ Last day of relevant Committee meeting

⁵ First day of the 7th month

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35 EXECUTIVE SUMMARY

36 To be added after finalisation of the Guideline

37 **1 INTRODUCTION**

38 Neonates are the group of children from birth up to and including the age of 27 days, including term
39 and preterm neonates. They represent a particularly vulnerable subgroup of the paediatric population.
40 Whilst they account for a low percentage of the total drug use in childhood, up to 90 % of medicinal
41 products are used unauthorised or off-label in this population, especially if treated on Neonatal
42 Intensive Care Units (NICUs).

43 The reasons why clinical trials of medicinal products have not been performed in neonates as in older
44 age groups are multiple, and they include the age-related difficulties in feasibility as well as the small
45 patient population, and especially the uniqueness of their diseases. The Regulation on Medicinal
46 Products for Paediatric Use (Regulation (EC) 1901/2006) is creating obligations with regard to
47 specially conducting clinical trials in order to meet the recognised need for authorised medicinal
48 products and the availability of information on the use of medicinal products for paediatric patients
49 including this age group. Clinical trials to investigate medicinal products in the neonatal population
50 thus have to address the needs of this population (or subgroups thereof, refer to section 9.1) which, for
51 example, arise from the following conditions that specifically affect the neonatal population.

52 However, neonatal studies encompass multiple difficulties, of which ethical issues, the high
53 vulnerability, technical difficulties, lack of self assessment, immaturity, prematurity, and the need for
54 specific formulations are examples of such complicating factors.

55 **2 SCOPE**

56 The guideline aims to provide guidance for the development of medicinal products for use in the
57 neonatal population. However, it cannot encompass all potential aspects applying to all medicinal
58 products in the various conditions affecting the neonate. In addition, the scientific development, rapid
59 changes and the emergence of medical innovations in this therapeutic area will require revisions of the
60 guideline and, on behalf of the sponsor or applicant, consideration of current scientific knowledge.

61 As well as due to the complexity of how to investigate medicinal products in the neonatal population
62 and the high vulnerability of the neonatal population, applicants are therefore strongly advised to seek
63 further expert opinion and European regulatory scientific advice in this regard.

64 This guideline shall be relevant to all investigations of medicinal products that include participation of
65 the neonatal population.

66 The guideline is based on several concept papers released by the Paediatric Working Party (PEG)
67 addressing the impact of immaturity of different organ systems when investigating medicinal products
68 in the neonate. It therefore contains specific aspects related to organ development that should be
69 considered during the development of medicinal products in the neonate.

70 **3 LEGAL BASIS**

71 This guideline should be read in conjunction with:

- 72 – Regulation on Medicinal Products for Paediatric Use (EC) 1901/2006 as amended by Regulation
73 (EC) 1902/2006
- 74 – Directive 2001/20/EC on the implementation of good clinical practice in the conduct of clinical
75 trials on medicinal products for human use
- 76 – ICH E11 Clinical Investigation of Medicinal Products in the Paediatric Population
77 CPMP/ICH/2711/99
- 78 – Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the
79 Paediatric Population CHMP/EWP/147013/04

- 80 – Guidelines on conduct of pharmacovigilance for medicines used by the paediatric population
- 81 EMEA/CHMP/PhVWP/235910/2005- rev.1
- 82 – Ethical Considerations for Clinical Trials Performed in Children – Recommendations of the Ad
- 83 Hoc Group for the development of implementing guidelines for Directive 2001/20/EC relating to
- 84 good clinical practice in the conduct of clinical trials on medicinal products for human use (draft)
- 85 – Reflection Paper on Formulations of Choice in Paediatric Population EMEA/196218/05
- 86 – Discussion Paper on the Impact of Renal Immaturity CHMP/PEG/35132/03
- 87 – Concept Paper on the Impact of Liver Immaturity CHMP/PEG/194605/05
- 88 – Concept Paper on the Impact of Lung and Heart Immaturity CHMP/PEG/114218/06
- 89 – Concept Paper on the Impact of Brain Immaturity CHMP/PEG/181377/06
- 90 – Guideline on Clinical Trials in small populations CHMP/EWP/83561/05
- 91 – Guideline on the Need for Non-Clinical Testing in Juvenile Animals on Human Pharmaceuticals
- 92 for Paediatric Indications CHMP/SWP/169215/05 (draft)
- 93 – Regulation No (EC) 141/2000 on orphan medicinal products
- 94 – Annex I to Directive 2001/83/EC, as amended
- 95 – Other relevant Agency (including ICH) Guidelines

96 **GUIDELINE TEXT**

97 **1 DEFINITIONS**

98 For the purpose of this guideline, the following definitions are used.

- 99 – Neonatal period: Period from birth up to and including the age of 27 days
- 100 – Gestational age (GA): Time between first day of last normal menstrual period and date of birth,
- 101 usually expressed in weeks; GA is defined at birth.
- 102 – Post-natal age (PNA) or chronological age: Age calculated from date of birth
- 103 – Post-menstrual age (PMA): Time between first day of last normal menstrual period and day of
- 104 assessment, that is, gestational age plus post-natal age
- 105 – Corrected age (of preterm neonates): Age calculated from expected date of delivery
- 106 – Preterm neonate: < 37 weeks of gestational age
- 107 – Low birth weight (LBW): Birth weight < 2500 g
- 108 – Very low birth weight (VLBW): Birth weight < 1500 g
- 109 – Extremely low birth weight (ELBW): Birth weight < 1000 g
- 110 – Small for gestational age (SGA): Birth weight below 10th percentile for gestational age

111 It might be appropriate to use different definitions or classifications depending on the context of use.
 112 For example, developmental issues of the neonate are often related to gestational age whereas birth
 113 weight based classification is often used in relation to dosing in the neonate. Post-conceptual age
 114 (time between day of conception and the date of assessment) should not be used because the day of
 115 conception is most often unknown.

116 **2 ORGAN MATURATION IN THE NEONATE**

117 Most organ functions are physiologically immature in the neonatal period. The degree of immaturity
 118 may be aggravated due to prematurity, intrauterine growth retardation or any potential pathologic
 119 condition affecting the neonate. Functional immaturity of physiological processes and organ function

120 predispose neonates to altered pharmacokinetics and pharmacodynamics, leading to potential
121 inefficacy or reduced safety of a drug in the neonate.

122 Maturation changes are rapid in the post-natal period, and the resulting high variability of the
123 neonates (both inter-individually and intra-individually) has to be considered when investigating
124 medicinal products for use in the neonatal population. Additionally, any drug administered to the
125 neonate may affect the ongoing maturation processes. If possible, points in time of major
126 developmental changes should be identified that could significantly influence drug exposure, safety
127 and efficacy. If adequate and possible, not only pharmacokinetic changes due to ongoing maturation
128 but also pharmacodynamic changes as a function of maturation itself should be investigated.

129 The following sections address specific issues of immaturity of different organ systems. It has to be
130 emphasised that in addition to the organs outlined below, several other organ systems (e.g. eye, ear,
131 haematopoietic or coagulation system) may show significant maturation during the neonatal period,
132 and this has to be taken into consideration as well. The sections should be viewed as a reminder of the
133 specific considerations in the neonates related to immaturity. The considerations and investigations
134 needed depend on the pharmacokinetic and pharmacodynamic characteristics of the drug investigated.
135 However, an isolated view of single organs should be avoided since organ systems and functions are
136 closely interrelated.

137 **2.1 Heart and lung**

138 The post-natal cardiopulmonary system adaptation marks the most dramatic changes during and after
139 birth. Some of these changes occur instantaneous with the first breath, whereas others occur within
140 hours or days after birth. In general, the impact of lung and heart maturation on PK/PD relationship
141 (e.g., closure of the ductus arteriosus) has to be considered.

142 Due to the complexity of anatomic and functional adaptation processes even subtle variations (e.g.,
143 through administration of drugs) can impede the smooth transition to extrauterine life. This may be
144 aggravated through congenital structural cardiac defects or any other condition affecting physiological
145 maturation.

146 As adequate cardiopulmonary function is paramount to maintain organ function in general (e.g., renal
147 blood flow, brain perfusion, liver function), any potential impact on either cardiac or pulmonary
148 function needs to be carefully monitored in neonatal clinical trials. The influence of cardiopulmonary
149 function as the basis to maintain hepatic drug metabolism and excretion as well as renal excretion has
150 to be considered. For the purpose of clinical trial protocols, it has to be considered that clinical
151 symptoms and signs of cardiopulmonary dysfunction in the neonate differ compared to older children
152 and adults. Distinct cardiac (e.g., patent ductus arteriosus) and pulmonary (e.g., respiratory distress
153 syndrome) conditions specific for the neonatal population may need to be taken into consideration
154 when planning a trial protocol. Stratification according to the clinical state or condition may be
155 appropriate in some cases.

156 As cardiovascular receptors (e.g., adrenergic) are often immature in the neonate, ongoing receptor
157 maturation has to be taken into account including potential desensitisation of receptors with ongoing
158 treatment. Dose adjustment, especially in maintenance therapy may need to be considered.

159 Specific adverse reactions may be seen due to the immaturity of the cardiopulmonary system of the
160 neonate, especially if congenital or concomitant diseases are superimposed. For instance, cardiac
161 malformations affecting the neonatal myocardium may increase the susceptibility to QT prolongation
162 and Torsade-de-Points.

163 **Monitoring of cardiopulmonary function**

164 Cardiopulmonary monitoring of hospitalised neonates is carried out on a routine basis and these
165 findings should be used and documented for the purpose of a clinical trial as appropriate. Less or non-
166 invasive measures should be used whenever possible (e.g., measurement of blood pressure, heart rate,
167 respiratory excursions and rate; pulse oximetry in at least one site, transcutaneous pO₂ measuring,
168 electrocardiogram [ECG], echocardiography, and Doppler sonography). Radiologic (e.g. X-ray, MRI)
169 and laboratory (e.g., blood gases, haematocrit) assessment may additionally be required and would
170 need to be synchronised with routine assessments and limited as much as possible.

171 **2.2 Central nervous system (CNS)**

172 Critical processes of brain development consist of neuronal proliferation, migration, organisation and
173 myelination. Two main phases can be distinguished with the first occurring between the 2nd and 4th
174 month of gestation, consisting of neuronal proliferation and generation of radial glia, and the second
175 phase between 5 months and 1 year of life, consisting of glial multiplication.

176 Transport across the blood brain barrier by both passive diffusion and by active transporters is age-
177 related and undergoes constant maturational changes in the neonate. This may contribute to a
178 significantly altered distribution of active substances or metabolites into the CNS with a potential
179 impact on both clinical efficacy and adverse effects. Medicinal products known or expected to be
180 substrate for specific transporters (e.g., P glycoprotein, Pgp) require specific consideration. Any
181 medicinal product interacting with glutamic acid and other neurotransmitters is expected to have an
182 effect on brain development in the neonate. This should be carefully considered and monitored where
183 possible.

184 Hypoglycemia is an important risk factor for perinatal brain injury. Due to the high metabolic rate and
185 the dependence on glucose as unique source of energy of the brain, any medicinal product affecting
186 glucose metabolism in the neonate may have an effect on the developing brain. This should be
187 carefully taken into consideration when planning a neonatal study.

188 Increased intracerebral bilirubin concentrations may lead to bilirubin encephalopathy and severe brain
189 damage (kernicterus). The pathogenesis of bilirubin encephalopathy is multifactorial and involves an
190 interaction between unconjugated bilirubin levels, albumin binding capacity, blood brain barrier
191 development and neuronal susceptibility to injury. Compounds with a presumed effect on any of these
192 factors may increase the risk of developing bilirubin encephalopathy. This should be carefully taken
193 into consideration when planning a neonatal study.

194 Autoregulation of cerebral blood flow is limited in the immature brain. Hyperoxemia and hypocapnia
195 (especially when associated), hypoxia as well as vasoactive substances may have a dramatic impact on
196 cerebral blood flow in the neonate during the first days of life.

197 **Monitoring of brain function**

198 Measures to monitor brain function include EEG (electroencephalography), amplitude-integrated EEG,
199 ultrasonography, Doppler sonography, auditory and visual evoked potential measurements (AEP,
200 VEP), cerebrospinal fluid (CSF) sampling, (functional) magnetic resonance imaging (MRI) and
201 positron emission tomography (PET). Use of invasive and risk-associated measures (CSF sampling,
202 PET) as well as sedation or anaesthesia of the neonate required for measures needs to be fully justified.
203 Any use of general anaesthesia for study purposes should occur in exceptional circumstances only, but
204 should not prohibit the development of medicinal products for anaesthesia.

205 **2.3 Kidney and renal function**

206 Renal clearance mechanisms include glomerular filtration (GFR), tubular secretion and reabsorption.
207 Glomerular filtration matures faster than the tubular function, and both depend not only on age and
208 maturational status but also on adverse factors occurring in the pre- and post-natal period, including
209 for example intrauterine growth retardation or administration of nephrotoxic drugs to the mother and
210 the neonate.

211 Due to the high renal vascular resistance in utero, GFR is significantly reduced during fetal
212 development. In addition, fetal tubular function is programmed for producing hypotonic urine
213 contributing to amniotic fluid formation. Due to haemodynamic changes during and just after birth,
214 GFR increases rapidly in the first two weeks of life. Afterwards, GFR corrected for body surface area
215 (BSA) increases more slowly to reach adult levels between 1 to 2 years of age.

216 Very low birth weight (VLBW) infants exhibit lower GFR values at birth and a slower pattern of GFR
217 development because the complete nephrogenesis is not achieved before 34 weeks of post-menstrual
218 age (PMA). This functional delay in getting sufficient GFR in very preterm baby has to be considered
219 when estimating infant renal elimination capacity in such a group of babies and stratification may be
220 necessary. Two subsets of preterm neonates should therefore be distinguished in neonatal clinical trials:

221 before and after 34 weeks of PMA. Before 34 weeks of PMA, only a small increase in GFR is
222 observed until the nephrogenesis is fully achieved. As a consequence, it should be noted that post-
223 natal improvements in GFR correlate with PMA rather than PNA alone.

224 Renal tubules are significantly immature in the neonatal period. This is based on both anatomic and
225 functional immaturity, poor peritubular blood flow, reduced urine concentrating ability and lower
226 urinary pH values. Maturation of tubular function is generally more protracted than GFR maturation.
227 The resulting functional glomerulotubular imbalance has to be considered when investigating drugs in
228 neonates and persists until tubular maturation is completed between 1 and two years of age. Function
229 of protein carrier systems at the renal tubular epithelium and their impact on renal elimination in
230 neonates is still largely unknown. Therefore medicinal products known to be excreted via active
231 tubular secretion require special attention when studied in neonates. As pointed out in different studies,
232 the organic pathway undergoes more rapid maturation for anions than that for organic cations.

233 Additionally, certain adverse drug reactions affecting the renal system may only be seen in preterm
234 infants (e.g. nephrocalcinosis in loop diuretics).

235 **Monitoring renal function**

236 Serum creatinine is elevated in the first days of life and reflects maternal creatinine and low GFR in
237 the neonate. In VLBW, the persistence of an elevated serum creatinine during the first weeks of life is
238 the result of a transitory process of tubular creatinine reabsorption.

239 Therefore, to monitor renal function serum creatinine is used after the first week of life in term infants
240 and after 4 weeks in very low birth weight infants. Before these times, intra-individual changes
241 (related to post-menstrual age) in serum creatinine are used as a guide to renal function.

242 The method of monitoring depends on the investigational drug, but should always be the least invasive.
243 Each approach should be individualised and justified based on the condition to be treated, the clinical
244 state of the neonatal population under investigation and the pharmacokinetic and pharmacodynamic
245 properties of the product under investigation. There are additional methods to monitor renal function
246 and toxicity, including diuresis (measuring nappy weight); also refer to the Discussion Paper on the
247 Impact of Renal Immaturity.

248 **2.4 Liver and hepatic function**

249 Hepatic blood flow, plasma protein binding and intrinsic clearance determining hepatic clearance
250 undergo significant post-natal changes. Most enzymatic microsomal systems responsible for drug
251 metabolism are present at birth and their activities increase with advancing post-natal and gestational
252 age. Rapid maturational changes occur during the first weeks of life. Hepatic clearance may be
253 influenced by premature birth, pathologic conditions of the neonate or administration of drugs to the
254 mother or to the neonate.

255 To predict the exact nature of these consequences requires an understanding of post-natal maturation
256 and main involved enzymes. The development of specific enzymes is partly described in the scientific
257 literature and may allow estimations of drug metabolism in the neonate. These data should be
258 considered when planning neonatal studies.

259 The main pathway responsible for metabolism may be different in neonates as compared to adults. The
260 applicant should consider this when assessing exposure margins of metabolites to the animals used in
261 preclinical studies and also when comparing human safety data obtained in adults and older children.
262 The relevant hepatic phase I and II metabolic pathways should be identified.

263 If pharmacologically active metabolites are known to be formed, potential differences in exposure of
264 such metabolites should be considered. If feasible, the applicant is encouraged to perform studies
265 investigating drug metabolism in vitro in neonatal hepatic material (microsomes, hepatocytes etc.).

266 In utero exposure to enzyme inducing agents (e.g., antiepileptic drugs, barbiturates, glucocorticoids)
267 and the potential to temporarily alter post-natal drug disposition need to be considered when planning
268 a study in neonates and in the interpretation of data.

269 **Monitoring of liver function**

270 If the drug investigated is likely to be eliminated mainly through hepatic metabolism, markers of
271 hepatic function could be included as covariates in the pharmacokinetic data analysis (e.g., in
272 population PK analysis) as well as included in the safety assessment. Monitoring could include
273 standard laboratory and imaging procedures.

274 **2.5 Gastrointestinal tract**

275 Data concerning maturational changes of the neonatal gastrointestinal tract that may influence drug
276 bioavailability are still limited.

277 Gastrointestinal absorption is influenced by factors such as tissue perfusion, surface area, gastric and
278 intestinal pH, intestinal mobility and transit time as well as maturation of transporters and receptors. In
279 principle, all these factors are reduced or immature in the neonate. The post-natal developmental
280 pattern of these factors may additionally be highly variable due to environmental factors (i.e., diet,
281 drug administration), genetic factors and underlying pathophysiology. Changes in bioavailability
282 during the early post-natal period have to be considered and need to be predicted as accurate as
283 possible in clinical trials including drugs administered orally.

284 Gastric pH is neutral at birth with gastric acid secretory capacity appearing after the first 24 to 48
285 hours of life. Post-natal increases in gastric acid production generally correlate with post-natal age and
286 adult levels are reached by approximately 2 years of age.

287 High gastric pH in the neonate may lead to increased bioavailability of weakly basic compounds and
288 reduced bioavailability of weakly acidic compounds. Additionally, in premature infants, gastric pH
289 may remain elevated due to immature acid secretion. This may lead to higher serum concentrations of
290 acid-labile drugs in the premature neonate.

291 As pancreatic and biliary functions are immature at birth, bioavailability of drugs requiring pancreatic
292 exocrine and biliary function may have reduced bioavailability. Both functions develop rapidly in the
293 neonatal period, requiring careful consideration of increased bioavailability of orally administered
294 drugs in neonatal clinical trials.

295 Reduced gastrointestinal motility may have unpredictable effects on drug availability in neonates. It
296 may reduce the rate of drug absorption or conversely improve drug bioavailability due to longer
297 retention times in the small intestine. Additionally, maturation of intestinal metabolising enzymes and
298 transport proteins remains largely unknown, further leading to the unpredictability of oral
299 bioavailability and intestinal first-pass effect of orally administered drugs in the neonate. Drugs
300 undergoing secondary metabolism and secretion into the gut, especially when glucuronidation with
301 enterohepatic recirculation occurs in adults and older children, may have different bioavailability and
302 exposure because of reduced glucuronidation and bacterial activity in the intestine of neonates.
303 Reduced gastrointestinal mobility that is often present in sick neonates is therefore particularly
304 important to consider.

305 Additionally, the susceptibility of neonates to necrotising enterocolitis (NEC) should be taken into
306 consideration when studying drugs administered orally, as any intestinal damage may increase the risk
307 of NEC especially in premature neonates.

308 **2.6 Immune system**

309 Lymphoid stem cells develop from precursors and differentiate into T, B or NK cells, as well as
310 Antigen presenting cells (APCs) depending on the organs or tissues to which the stem cells traffic.
311 Indeed, both the initial organogenesis and the continued immune system cell differentiation occur as a
312 consequence of the interaction of a vast array of lymphocytic and microenvironmental cell surface
313 molecules and proteins secreted by the involved cells. De novo T-cell generation requires a functional
314 thymus. The current paradigm is that the human T-cell repertoire is established during late fetal
315 development and that, by the time of birth, thymectomy does not cause immediate immune deficiency.
316 Thymic epithelial cells - the component of the thymus relevant for T-cell production and selection -
317 involute rapidly after birth. Compared with adult T cells, neonatal T cells secrete increased levels of
318 interleukin-10 (IL-10) following stimulation, but reduced levels of many other cytokines, including

319 IL-2, IL-4, IL-8, interferon gamma (IFN-gamma), transforming growth factor beta (TGF-beta) and
320 tumor-necrosis factor alfa (TNF-alfa).

321 Although the fetal immune system has the potential to respond to large numbers of foreign antigens,
322 few foreign antigens are present in utero and cells of the immune system are therefore, primarily
323 “naïve” at birth. The neonate is, in part, protected against disease by maternal immunoglobulins (Ig).

324 Maternal IgG, in particular IgG₁, are actively transported across the placenta before birth prevalently
325 mainly in during the last 4 weeks of term gestation, and maternal secretory IgA are present in breast
326 milk and colostrum. These passively acquired antibodies provide protection against pathogens to
327 which the mother was immune. However, the neonatal/infant period is marked by an increased
328 susceptibility to infections: protection provided by passively transferred antibodies is short-lived since
329 declines during the first few months of life. More importantly, maternal antibodies offer limited
330 immunologic protection when compared with protection afforded by an infant’s active immune
331 response. Active adaptive immunity can be readily generated in the newborn and this includes the full
332 range of B-cell responses with the production of IgM, IgG and IgA, as well as the development of
333 helper T-cell (Th) and cytotoxic T-cell responses.

334 Indeed, neonates can produce specific Th-cell subsets, including Th1-type cells that participate in cell-
335 mediated immune responses and Th2 type cells that are primarily involved in promoting B-cell
336 responses.

337 The innate immune mechanisms also mediate the protection against infections during the first months
338 of life. Natural antibodies such as IgM, NK activity as well as toll-like receptors mediated cell
339 activation has been shown to play a role in development of adaptive immunity and to serve as a bridge
340 between antigen non-specific and antigen-specific immune responses.

341 In addition, bacterial colonisation from maternal and environmental microflora is an important
342 determinant of the induction of sub-chorial innate immunity and of adaptive immunity later. This step
343 is crucial to allow diet antigen tolerance induction. Inadequate interaction between bacteria and
344 enterocytes may be responsible for misbalancing the homeostasis between tolerance and activation; in
345 addition, antibiotic medicinal products may impact on bowel colonisation. Any such impact on gut
346 colonisation should be divided according whether it is temporary or permanent.

347 These complex interactions and the interference of maternal antibodies have to be considered when
348 evaluating the effect on immune response of immunomodulatory drugs both in terms of
349 immunosuppression and immune activation.

350 **Monitoring of immune functions**

351 Antibody response can readily be detected upon challenge in neonates provided to take into account
352 the presence of interfering maternal antibodies. Modern multiparameter cytofluorimetric technology
353 can be employed to assess not only the number of immune cells but also some immune functions such
354 as cytokine production or cytolytic activity. However an effort to develop microassays has to be done
355 to truly assess the different pattern of immune responses in the neonate and in infants in the first years
356 of life. Molecular techniques such as spectratyping for T and B cell repertoire assessment can also be
357 of value.

358 **2.7 Body composition**

359 Changes in body composition during the neonatal period are important factors for altered
360 pharmacodynamic and pharmacokinetic characteristics. Body composition correlates with both
361 gestational and post-natal age, and it continues to change significantly during the first years of life.
362 Age related changes in fat, muscle and total body water composition may produce significant
363 quantitative changes in the volume of distribution, peak plasma concentrations and half-lives. For
364 instance, total body water is highest in the newborn and decreases substantially in the first 4 months of
365 life. On the contrary, the amount of body fat is low at birth and increases progressively in the first
366 months of life.

367 **3 CONDITIONS AFFECTING SPECIFICALLY THE NEONATAL** 368 **POPULATION**

369 Neonates frequently suffer from conditions that are specific for this subset of the paediatric population,
370 for example respiratory distress syndrome (RDS) or patent ductus arteriosus (PDA). In addition,
371 neonates hospitalised on NICUs often suffer from multiple concomitant conditions, requiring
372 administration of a combination of medicinal products resulting in a high risk of drug interactions.
373 Additionally, adverse reactions in neonates, especially in preterms may trigger specific complications,
374 as for example in relation to susceptibility to necrotising enterocolitis (NEC) or retinopathy of
375 prematurity (ROP). As a further complicating factor, in utero growth retardation may affect
376 pharmacokinetics and pharmacodynamics of drugs at birth and therefore may change the safety and
377 efficacy profile of drugs used in the neonatal period.

378 With more experience, disease specific guidelines on how to investigate medicinal products in the
379 neonatal population may become available.

380 **4 TIMING OF DEVELOPMENT OF MEDICINAL PRODUCTS IN** 381 **NEONATES**

382 The timing of studying a medicinal product in the neonate will depend on the seriousness and
383 uniqueness of the condition to be treated as well as on the availability of alternative treatment options,
384 the potential benefit of a new product, and the target population. Sponsors should refer to ICH
385 Guideline E11.

386 **5 DATA REQUIRED BEFORE THE FIRST ADMINISTRATION TO A** 387 **NEONATE IN A CLINICAL TRIAL**

388 If possible, clinical data should always be obtained in the least vulnerable population. Depending on
389 the condition, the new product, the target population and further factors according to section 2.1 of the
390 ICH Guideline E11, initial tolerability, PK and safety data should be collected in adults before
391 initiating studies in the neonatal population.

392 If older children are affected by the same disease or another disease for which the medicinal product
393 may be of use, in general older (less vulnerable) paediatric age groups should be studied before
394 studying the product in the neonatal population.

395 For conditions exclusively found in neonates, the development should primarily be made in neonates.
396 However, also in such condition, the first studies in man should, if possible, be done in healthy adult
397 volunteers. Sponsors should refer to ICH Guideline E11.

398 **5.1 In vitro data**

399 In order to predict the in vivo situation as much as possible (i.e., as regards efficacy, pharmacokinetics,
400 safety), in vitro studies on human non-terminally differentiated cells or cell cultures (fetal or neonatal)
401 may provide relevant additional information. Examples include enzyme activity, receptor expression
402 and mediator modulation.

403 **5.2 Animal data**

404 The conventional nonclinical studies should be performed including pharmacokinetic, primary
405 pharmacodynamic, safety pharmacology, single- and repeated dose toxicity, genotoxicity,
406 reproductive and developmental toxicity, including peri-/post-natal toxicity testing (e.g., diaplacental
407 exposure) and local tolerance studies. In addition to these conventional nonclinical studies, juvenile
408 animal data should be provided if feasible. The limitations of species specificity should be taken into
409 account. Finding adequate juvenile animal models with similar organ maturation is challenging.
410 Available options should be investigated in depth, including whether relevant data can be obtained
411 from peri-/post-natal studies, e.g. by optimising the design of such studies. Juvenile toxicity studies
412 will be necessary if available data are insufficient, and if feasible. If not, a scientifically data based

413 justification should be provided. This is addressed in the Guideline on the Need for Non-Clinical
414 Testing in Juvenile Animals on Human Pharmaceuticals for Paediatric Indications.

415 **6 FORMULATIONS AND ROUTE OF ADMINISTRATION**

416 The choice of formulation and route of administration should depend on the condition to be treated
417 and the clinical state of the neonate. Age-appropriate formulations using appropriate excipients must
418 be developed to avoid extemporaneous preparations, even more so for neonates. Novel formulations
419 should be evaluated through preclinical studies and in adults or older children as appropriate before
420 consideration for administration to neonates.

421 Medication errors in neonatal practice are commonly due to use of inappropriate formulations
422 requiring calculation and measurement of very small volumes or multiple dilutions. Prescribing
423 software may not be appropriate for neonatal use. Excipients used for adults and older children may be
424 toxic in neonates because of immature metabolism and elimination. The salt of the active ingredient
425 and the chemical nature of the preparation must be carefully considered to avoid administration of
426 excessive amounts of electrolytes.

427 In general, the IV route will normally be used in clinically unstable term and preterm neonates.

428 When developing protocols for neonatal trials, devices designed for IV administration to neonates
429 must be selected and specified. Account must be taken of the potential lag time between injection and
430 delivery of the drug to the blood circulation. Administration of the complete dose must be ensured.

431 Drug preparations must allow accurate measurement and administration. The need for additional
432 dilution and/or flushing of devices may be important for effective administration and in avoiding
433 thrombophlebitis and acute systemic effects but must take account of fluid and electrolyte balance.
434 Local tolerance and toxicity of the drug preparation must be investigated (see also section 5.2) and
435 every effort should be made to administer isotonic preparations. The volume to be administered should
436 be as small as possible and as compatible with these requirements.

437 Sick neonates may receive multiple drug infusions and bolus injections with limited opportunity for
438 physical separation. IV feeding is common and there may be high concentrations of macro- and
439 micronutrients, especially calcium and phosphate. There is significant risk of physical and/or chemical
440 incompatibility with the investigational preparation. Potential incompatibilities must be studied and
441 strategies developed to avoid problems during administration. Conversely, positive recommendations
442 with regard to compatibilities would be most helpful to the user of the product.

443 Environmental conditions of the neonatal unit, for example temperature, humidity and ultraviolet light
444 may affect drug stability and should be investigated.

445 Other routes of administration may be required or may be suitable. Their use should be justified.

446 Oral administration may be appropriate for some medications for use in the neonatal population, but
447 there is still lack of data on absorption and safety (see also section 2.5). Such preparations are most
448 likely to be liquid dosage forms and the following considerations might apply:

- 449 – The volume to be administered should be kept as small as possible.
- 450 – In order to avoid such excipients as preservatives, antioxidants etc and eliminate microbial
451 contamination, a sterile product should be considered.

452 In case of possible solid dosage forms, e.g. granules, powders etc., unit dose presentations would be
453 preferable. When microbial contamination is an issue, the product should be presented as a sterile
454 product. For oral administration, the way of feeding (e.g., feeding tube), the time intervals and
455 amounts of feeding (i.e., the actual feeding patterns) have to be considered and specified.

456 Rectal administration is not commonly used in this age group. If considered it must be fully evaluated
457 for safety and efficacy.

458 Topical administration may be necessary or suitable for local or systemic effect. Account must be
459 taken of skin immaturity and maturation, especially in preterm neonates, and the large surface area to
460 weight ratio which all predispose to systemic toxicity. There may be increased systemic absorption
461 and toxicity from eye, nasal and other preparations intended for local effect.

462 Intramuscular injection is not usually a route of choice for drug administration because absorption may
463 be slow and unpredictable, varying with postnatal age and clinical state; injections may be painful and
464 cause tissue damage. If the IM route is considered its use must be justified.

465 The above text highlights the main principles which should be kept in mind prior to the conduct of
466 clinical trials in neonates. However, it is not intended to provide exhaustive information on
467 formulation aspects to be considered when developing products to be used in clinical trials in neonates.

468 **Comparisons of different formulations**

469 If a formulation is significantly changed during development for neonatal use, comparison of
470 bioavailability may be required. Such studies will usually be performed in adults or older children but,
471 if not representative for neonates, additional PK studies may be needed in neonates to ensure
472 appropriate systemic drug exposure. Multiple-dose studies may be required to ensure appropriate
473 treatment and the approach used should be carefully considered and justified depending on the clinical
474 situation and drug characteristics. Urine sampling could be used as a partial or complete replacement
475 of blood sampling (see also section 9.6). A similar approach should be taken in situations where a
476 completely new neonatal formulation has been developed with little or no clinical efficacy and safety
477 data using the specific formulation. Data on local tolerability should also be collected if the route of
478 administration is changed or if there are major changes in formulations administered by the same route.

479 **7 DOSE-FINDING**

480 In general, most drugs are developed for adults and older children before they are developed for the
481 neonatal population. All relevant pre-clinical and clinical data in adults and children should be taken
482 into consideration to find a safe starting dose in neonates. PK / PD modelling techniques, using age
483 appropriate and validated biomarkers, need to be considered to find the optimal dose. Existing
484 physiologically based pharmacokinetic models to predict pharmacokinetic characteristics in the
485 neonatal population may be considered if appropriate.

486 The modelling of the influence of maturation on PK and on the PK / PD relationship may be
487 considered to predict the changes in dosing as a function of age. Applicability of these models would
488 need to be justified and new models might need to be developed. Where the medicinal product belongs
489 to a chemical / pharmacological class including products already studied in neonates or older children,
490 all relevant data should be considered.

491 Both body surface area and weight need to be investigated for best correlation with PK data and for
492 best use as dosing reference; taking into account that body weight is likely to be more user friendly
493 and that various covariates have to be considered (see following section). Depending on the duration
494 of treatment, the individual maturation of a patient may be extensive and the dose may need to be
495 adjusted over time (see section 9.4).

496 **8 PHARMACOKINETIC STUDIES AND PK/PD STUDIES**

497 Reference is made to the “Guideline on the Role of Pharmacokinetics in the Development of
498 Medicinal Products in the Paediatric Population”, especially section 4.1.

499 Pharmacokinetic information is important to support adequate dosing in subpopulations of the
500 clinically studied population and to assess the potential for clinical relevance of toxicity findings in the
501 preclinical studies. In neonates, however, pharmacokinetics alone is of limited value in neonates for
502 extrapolating efficacy and safety from other patient groups and extrapolation of efficacy will in
503 general need PK/PD monitoring.

504 A population PK approach is preferable due to the importance of finding covariates related to dose-
505 individualisation between individuals and over time in the maturing individual. The analysis can be
506 made on rich and/or sparse data depending on the number of patients available and the possibility of
507 developing highly sensitive analytical methods where very small sample volumes could be used. The
508 initial model could be based on rich data of a limited number of individuals and on other prior
509 information, followed by a population PK approach.

510 It should be noted that population PK and modelling of oral administration require extra cautious
511 consideration in the neonatal population as there may be marked absorption differences in neonates as
512 compared to other age groups as well as very prolonged absorption in a subgroup of individuals.

513 In cases where C_{max} is clinically important for safety or efficacy reasons, efforts should be made to
514 characterise this parameter satisfactorily due to the differences in volume of distribution between
515 neonates and older children. If possible, the protein binding of highly protein bound active substances
516 should be assessed to enable the measurement of free plasma concentrations. Immature expression of
517 carrier proteins should also be considered. Special consideration should be given to drugs which are
518 highly protein bound and fast metabolized in adults, since major differences can be assumed in
519 newborns, as synthesis of binding proteins such as albumin could be lower in the neonate with
520 consequences on drug binding and free bilirubin. The need for differentiation between a loading dose
521 (large Vd) and smaller maintenance doses (low total body clearances) as important, e.g., for
522 methylxanthines, aminoglycosides, and anticonvulsants, has to be identified.

523 Effort should be made to include the determination of potential covariates in the studies (PNA, PMA,
524 GA, weight, body surface area [BSA], renal function, concomitant use of drugs, S-bilirubin, repeated
525 feeding and feeding patterns etc.) for allowing covariates to be identified which may allow satisfactory
526 dose individualisation. Adjustments of the dose by covariates (e.g. bodyweight, BSA) should usually
527 be based on the covariate with the highest correlation to the relevant PK parameters. However, the
528 difficulties in determining the covariate should be taken into account. The determination of BSA is
529 difficult in neonates and other covariates should be considered if their use gives an adequate dosing.
530 Titration based on plasma concentration or a clinical safety or efficacy marker should also be
531 considered. This is further described in the Guideline on the Role of Pharmacokinetics in the
532 Development of Medicinal Products in the Paediatric Population.

533 Neonates treated in hospital and especially on NICUs often receive multiple drugs to treat different
534 conditions. Therefore, any known or potential interactions of the medicinal product investigated
535 should be carefully considered when planning a clinical study as well as during data analysis.
536 Concomitantly used drugs should be included in the population pharmacokinetic analysis. In general,
537 formal interaction studies should be performed in adults. However, if the main enzymes involved in
538 the elimination of the drug are different in the neonate, results of adult interaction studies investigating
539 effects of other drugs on the investigated medicinal product can not be directly extrapolated to
540 neonates. In these cases, estimations based on *in vitro* metabolism data as well as other sources of
541 information should if possible be performed. If a dosing recommendation is needed for a commonly
542 used drug combination and if an interaction is expected, specific pharmacokinetic interaction studies
543 should be considered.

544 **9 SPECIAL ASPECTS OF CLINICAL TRIAL DESIGN IN NEONATES**

545 As for all clinical trials all measures to avoid bias should be included in trials performed in neonates.
546 Therefore uncontrolled trials should be avoided in principle for demonstration of efficacy. They have
547 limited usefulness for the demonstration of safety. On the other hand for randomised trials, in
548 particular those using a placebo, there should be equipoise (genuine uncertainty) at the beginning of
549 the trial and no participants should receive care known to be inferior to existing treatments.

550 The size of a trial conducted in neonates should be as small as possible to demonstrate the appropriate
551 efficacy with sufficient statistical power. Adaptive, sequential, Bayesian or other designs may be used
552 to minimise the size of the clinical trial. However, a balance between the need to stop recruitment
553 early and the need to obtain reliable safety information should be aimed at.

554 In neonatal studies measures to reduce and prevent invasive procedures and pain are needed. But non-
555 invasive measures or surrogate markers require careful validation.

556 In addition, clinical trials in neonates should be carried out in neonatology experienced centres with
557 relevant expertise and with appropriate resources, in order to ensure optimum professional conditions
558 for the protection and medical support of the neonates.

559 **9.1 Age and further stratification criteria**

560 Taking into account age classes is of particular importance when recruiting patients within the
561 clinically relevant age interval to optimise the evidence the potential influence of maturation. However,
562 during data analysis, the use of age as a continuous co-variable is recommended whenever possible for
563 the same reason.

564 Depending on the medicinal product concerned and the disease to be treated, stratification of the trial
565 population might be appropriate or necessary. Frequently, stratification by term gestation is needed in
566 clinical trials, as PK and PD properties differ between preterm and full-term neonates. The same
567 applies to age and post-menstrual age (PMA). For instance, stratification regarding neonatal
568 nephrogenesis should be before and after 34 weeks of PMA (see 2.3).

569 The following subgroups within the neonatal population should be recognised as distinct, and criteria
570 for stratification should be considered accordingly. In addition, some of the conditions affecting
571 neonates are associated with profound changes in body function, such as about 20 % larger energy
572 requirements in bronchopulmonary dysplasia (BPD), which may require consideration in a trial.

573 – SGA or not; hypertrophy or not

574 – ELBW, VLBW, and LBW

575 – GA: < 26 weeks, 26 - 29 weeks, 30 - 33 weeks, 34 - 36 weeks, 37 - 40 weeks, > 40 weeks

576 Additionally, the importance of further criteria (from the course of medical treatment) such as the
577 following may need to be identified.

578 – Ventilation (if any, days and type of ventilation, inspired oxygen fraction) and interventions such
579 as pulmonary or cardiopulmonary resuscitation or assistance

580 – Existence and haemodynamic significance of patent ductus arteriosus Botalli or other cardiac
581 problems

582 – Antenatal treatment (e.g., with glucocorticosteroids, antibiotics, or blood products)

583 – Maternal diseases (diabetes mellitus, autoimmune diseases etc.)

584 – Use of drugs with haemodynamic effect (e.g., catecholamines), drug with effect on apnea-
585 bradycardia (e.g., caffeine), and drugs for relaxation, pain treatment, or sedation (e.g., morphine)

586 – Number and type of infections, days of incubator care and incubator temperature adjustments,
587 course of enteral feeding

588 – Volume and time of (all) blood sampling

589 **9.2 Endpoints and outcome measures**

590 For use in clinical trials in neonates, there is a need to elaborate clinically relevant primary endpoints,
591 linked to the conditions and prospects specific to preterm and term neonates. In addition, the need for
592 establishing age appropriate surrogate endpoints should be considered.

593 For the distinct diseases in neonatology, stringent and harmonised definitions should be detailed in the
594 protocol and used within a trial, especially when used as an endpoint. Endpoints should be assessed
595 using validated procedures for measurement or judgement.

596 The known complications and sequelae of prematurity (e.g. intraventricular haemorrhage [IVH], NEC,
597 ROP, BPD) as well as survival should be evaluated at least as secondary endpoints in trials that
598 include the neonatal population. In general, additional endpoints related to long-term physical and
599 mental development should be considered.

600 **9.3 Pharmacogenetics**

601 The relationship between phenotype and genotype may be completely different in the neonate as
602 compared to other patient groups.

603 If feasible, blood may be collected for future pharmacogenetic analysis.

604 If target genes of interest can be identified, pharmacogenetic analyses of these genes are encouraged.
605 If there are important pharmacogenetic differences affecting pharmacokinetics, efficacy and safety of
606 the drug in the adult populations, pharmacogenetic analysis of the target genes is recommended in
607 neonates. In such cases, the time-dependency (maturation) of the relationship between genotype and
608 phenotype may need to be described.

609 **9.4 Dosage adjustment over time**

610 Within days in the life of preterm and term neonates, there may be large physiological and / or
611 pathological changes in body weight, body surface area, and body composition, as indicated above.
612 For example, physiological post-natal weight loss may be more than 10 % of birth weight, and body
613 weight in preterm neonates may increase threefold during post-natal medical care.

614 Consequently, there is a need to continuously re-calculate and adjust dosages of investigational
615 medicinal products on the basis of actual weight (or other relevant covariates) or on the basis of results
616 from therapeutic drug monitoring, because fixed or perpetuated dosages are most probably inadequate
617 in terms of efficacy and safety.

618 **9.5 Placebo and active comparator**

619 Use of placebo in neonates is more restricted than in adults and older children. However, the use of
620 placebo is often needed for scientific reasons, including in paediatric trials with neonates. Placebo may
621 be warranted in children as in adults when evidence is lacking. As the level of evidence in favour of an
622 effective treatment increases, the ethical justification for placebo use decreases. Placebo use is not
623 equivalent to absence of treatment, for example placebo could be used on top of standard care. In all
624 cases, its use should be assorted with measures to minimise exposure and avoid irreversible harm,
625 especially in serious or rapidly evolving diseases.

626 As the number of approved drugs for the neonate population is limited, a comparator may have to be
627 chosen that is not approved for the indication. Medicinal products devoid of a marketing authorisation
628 may be considered suitable as controls if they represent evidence-based standard of care.

629 As appropriate, a rescue treatment to be used in case of insufficient efficacy should be employed
630 whenever possible in a planned manner.

631 Reference to the draft document on ethical considerations for clinical trials on medicinal products with
632 the paediatric population is made in this regard.

633 **9.6 Blood sampling**

634 Preterm and term neonates have very limited blood volume, are often anaemic due to age and frequent
635 sampling related to pathological conditions. The fact that they receive blood transfusions (or iron or
636 erythropoietin supplementation) must not be used as a convenience for increased volume or frequency
637 for blood sampling.

638 To limit the need for blood samples, the use or special development of microassays, of non-invasive
639 techniques, and of alternative methods is encouraged, like microdialysis, measuring drug levels in
640 saliva, urine etc., if shown to reflect systemic exposure. However, the burden associated with some
641 alternative methods (such as repeated skin taping of urine collection bags) should be recognised and
642 weighed against expert blood sampling.

643 Monitoring of actual blood loss is routinely required in preterm and term neonates. Expected blood
644 loss is to be detailed in the trial protocol. Sampling should be performed by trained staff. The number
645 of attempts for sampling should be limited. Timing of sampling and number of sampling attempts
646 should be defined in the protocol. Timing of sampling should be co-ordinated as far as possible to
647 avoid repeat procedures and to avoid repeat sampling during the day in order to minimise pain and
648 distress, and the risk of iatrogenic complications.

649 The following blood volume limits for sampling are recommended (not evidence-based). If an
650 investigator decides to deviate from these, this should be justified. Per individual, the trial-related
651 blood loss (including any losses in the manoeuvre) should not exceed 3 % of the total blood volume

652 during a period of four weeks and should not exceed 1 % at any single time. The actual situation of the
653 neonate (sleep/activity, severity of anaemia, and haemodynamic state) must permit such blood
654 sampling. The total volume of blood is estimated at 80 to 90 ml/kg body weight; 3 % corresponds to
655 about 2.4 to 2.7 ml blood per kg body weight.

656 **9.7 Study analysis**

657 When there is a limited number of data, it is imperative that the most efficient and informative
658 analytical methods should be used. Many of these methods involve ‘statistical modelling’. Such
659 models usually make assumptions about the data or the form of the treatment effect. With few data,
660 these assumptions may not be testable or verifiable. However, assumptions add to the data so that
661 more complex statistical models give us more information than simple descriptive statistics. Hence,
662 sensitivity analyses consisting of various analyses/models should be presented, which may make
663 different assumptions about the data. Such sensitivity analyses should be pre-planned. Then it can be
664 seen if the conclusions are heavily reliant on the model assumptions or if, in fact, they are robust to a
665 variety of plausible assumptions.

666 Adjustment for baseline variables may greatly improve the efficiency of an analysis. Factors used to
667 stratify the randomisation in a study should be used to stratify the analysis. Including prognostic
668 variables in a model can greatly enhance the precision of a treatment effect. Also refer to section 9.1
669 on age, stratification and confounding criteria.

670 Repeated measurements over time - or in different body locations - may also improve the efficiency of
671 an analysis. A commonly encountered problem in the analysis of such data is the non-independence
672 between observations. Non-independence occurs when data fall into groups or clusters, e.g. in
673 different body locations or in longitudinal studies. There are different methods available to analyse
674 clustered dependent data e.g. the Generalized Estimated Equations (GEE) method, Hierarchical Linear
675 Models or Mixed-effects models. These modern statistical approaches take the correlation within
676 subjects into account and can also allow an unequal number of observations per subject (e.g. caused by
677 missing values) so that valid inferences can be assured.

678 Bayesian methods are a further means of ‘adding assumptions’ to data. They are a way to formally
679 combine knowledge from previous data or prior ‘beliefs’ with data from a study. Such methods may
680 be advantageous when faced with small datasets, although introducing prior beliefs is often a concern
681 in drug regulation. As with sensitivity analyses mentioned above, a variety of reasonable prior
682 distributions should be used to combine with data from studies to ensure that conclusions are not too
683 heavily weighted on the prior beliefs. Reference is made to the Guideline on Clinical Trials in Small
684 Populations.

685 **9.8 Pain and distress**

686 As most investigations and procedures carry the risk of pain for the neonates, pain should be prevented,
687 and if unavoidable evaluated, monitored and treated appropriately. Evaluating and monitoring the
688 level of pain may be difficult in the neonate, as scales are based on physiological parameters that can
689 be affected by concomitant diseases and procedures. However, the development and / or use of
690 validated scales is recommended, for example, the Premature Infant Pain Profile (PIPP) or the
691 Neonatal Infant Pain Scale (NIPS) scale for the assessment of pain.

692 Exposure to pain and in particular repeated pain may trigger both an altered hypothalamic-pituitary-
693 adrenal-axis reactivity and an increase in NMDA/excitatory amino acid activation resulting in damage
694 to developing neurons. Most clinical parameters should be measurable using preferably non-invasive
695 techniques such as ECG cardiac monitoring, brain function monitoring, oxygen saturation (from pulse
696 oximetry), urine collection, non-invasive blood pressure measurement, ultrasonographic assessment of
697 the heart and lung circulation. For instance, transcutaneous measurement of PO₂ or PCO₂ is easily
698 performed using a single sensor in preterm and term neonates; however, it entails the risk of skin burns
699 associated with heating temperature and change intervals.

700 Blood sampling should be limited in number of samples and volume, and standard clinical care and
701 sampling should if possible be coordinated (see also section 9.6). Pain due to unavoidable blood

702 sampling should be pre-emptively treated whenever possible, using oral glucose or possibly topical
703 anaesthesia, if evaluated in the age group.

704 Also refer to the respective sections of the draft document on ethical considerations for clinical trials
705 on medicinal products with the paediatric population. Sponsors are advised to also refer to the
706 Recommendations of the Working Group on Implementation of the Clinical Trials Directive
707 2001/20/EC.

708 **9.9 Safety monitoring**

709 As a general recommendation for hospitalised infants in a trial, vital signs should be monitored
710 continuously, and related events should be registered according to neonatal definitions (apnea-
711 bradycardia; sustained bradycardia, tachycardia, desaturation, hypotension; fever, hypothermia etc.).

712 When there are no satisfactory blood safety data on the investigational medicinal product available,
713 and when the trial does not require more extensive tests for pharmacological investigations, the
714 function of the important and highly metabolically active organs bone marrow, liver, and kidney
715 should be monitored using blood sampling for respective laboratory values (for example, full manual
716 differentiated blood count including normoblasts and reticulocytes; glucose, AST, ALT, bilirubin;
717 creatinine, electrolytes).

718 **Assessment of trial participants at entry / end of trial**

719 In the neonatal population, adverse reactions, long-term effects, as well as general health-related
720 problems may not be obvious, but should be searched for and may become evident by thorough
721 clinical examination. Depending on the type of investigation and on the medicinal products, it is also
722 recommended to consider that all trial participants be examined using age-appropriate
723 neurodevelopmental (e.g., Dubowitz neonatal assessment at discharge, later Griffith test, Bayleys
724 scales) and auxiological (weight, length, head circumference) scales, at least at the beginning and at
725 the end of the trial, and during follow-up visits, where appropriate. Also, non-invasive and non-
726 burdening examinations such as objective hearing tests (otoacoustic emissions and distortions spectra
727 analysis), amplitude-averaging EEG recordings and laboratory parameters as mentioned in the
728 following sections should be documented.

729 **10 PHARMACOVIGILANCE AND LONG-TERM FOLLOW UP OF** 730 **SAFETY**

731 The challenging task of pharmacovigilance and follow-up in terms of duration and type depends on
732 the product itself, the target organs, the duration of exposure and other risk factors for sequelae. The
733 potential for adverse drug reactions occurring later in life should be monitored as neonates may have
734 been exposed to medicinal products at a sensitive period in terms of organ maturation. Only a small
735 number of neonates is likely to be included in rather short term trials, thus long-term adverse reactions
736 may not be detected and would require appropriate pharmacovigilance approaches and particularly
737 pharmacoepidemiological studies.

738 The difficulty to obtain data on short-and long-term effects of medicinal products on the developing
739 brain, as effects may become apparent only later in life, increases the level of requirements for trials of
740 medicinal products in neonates. Therefore, long term monitoring for medicinal products affecting the
741 CNS may be required (e.g., cognition assessment at school age).

742 Further important tools to evaluate pharmacovigilance aspects in neonates are:

- 743 – Access to epidemiological databases
- 744 – Case definitions for expected rare ADRs in neonates or paediatrics
- 745 – Description of standard of care and consequently standards of diagnostic and observation as a
746 supplement to the study design.
- 747 – Evaluation of potential risks according to knowledge from preclinical trials in juvenile animal
748 model or early phase clinical trial in adults.

- 749 – Attempt to define expected ADRs based on the knowledge of the proposed potential risk.
- 750 – Enhanced ADR reporting environment (educating parents when considering long term, delayed
751 onset ADRs)
- 752 – Postmarketing Trial as cohort or case control setting
- 753 However, a multidisciplinary approach is required to increase the awareness to a more proactive
754 involvement of physicians in Pharmacovigilance aspects in neonates and consequently to enhance the
755 safety profile of drugs at all stages of development covering the clinical challenges of the whole
756 paediatric population.
- 757 Reference is made to the Guidelines on conduct of pharmacovigilance for medicines used by the
758 paediatric population.

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