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4 **Guideline on immunogenicity assessment of monoclonal**
5 **antibodies intended for in vivo clinical use.**

6 Draft

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35 **Executive summary**

36 This guideline addresses issues relating to the unwanted immunogenicity of monoclonal antibodies
37 intended for clinical use. These include the variability of immunogenicity of mAbs and its
38 consequences, prediction and minimizing immunogenicity, the clinical consequences of
39 immunogenicity, assay related problems, assessing neutralizing antibodies induced by monoclonal
40 antibodies and consideration of a risk-based approach for the evaluation of immunogenicity of
41 monoclonal antibodies.

42 **1. Introduction (background)**

43 Unwanted immunogenicity can be a significant problem in the treatment of patients with therapeutic
44 biologicals. The importance of the unwanted immunogenicity problem has led to the preparation and
45 adoption of the 'Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic
46 Proteins' by the CHMP (adopted April 2008, referred to henceforth as 'the general guideline'), which in
47 principle is applicable to monoclonal antibodies (mAbs). However, some specific aspects of
48 immunogenicity are exclusively or primarily relevant for mAbs, novel mAb derivatives (eg Fab
49 fragments, scfv, nanobodies, minibodies) or biosimilar mAbs and these are addressed in this guideline.

50 Monoclonal Antibodies (mAbs) comprise a large important class of therapeutic biologicals. The range of
51 clinical indications with potential for treatment with mAbs is very wide. Many mAb products are known
52 to be associated with unwanted immunogenicity and in some cases the immunogenicity causes
53 impaired clinical responses or rarely serious adverse reactions which require clinical intervention. The
54 wide range of mAbs in development, and approved for different clinical indications precludes specific
55 guidelines that are pertinent to all situations. This guideline addresses the major quality and clinical
56 aspects that are important to consider in order to adequately address the problems with detection of
57 and risk related to the development of an immune response to the particular mAb in the particular
58 clinical indication sought.

59 **2. Scope**

60 The general principles adopted and explained in this document mainly apply to the development of an
61 unwanted immune response against a therapeutic or in vivo diagnostic mAb in recipients and how to
62 systematically evaluate this. The guideline applies to mAbs, their derivatives, and products of which
63 they are components, e.g., conjugates.

64 This guideline should be read in conjunction with other relevant guidelines, e.g.:

- 65 • Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins
- 66 • Guidelines on similar biological (biosimilar) medicinal products
- 67 • Guideline on Development, Production, Characterisation and Specifications for Monoclonal
68 Antibodies and Related Products
- 69 • European Pharmacopeia monograph on monoclonal antibodies
- 70 • Guidelines on comparability of biotechnology-derived medicinal products after a change in the
71 manufacturing process.

72 This guideline is primarily aimed at products at final development stage (e.g. marketing authorization
73 application stage). However, many of the principles are relevant to earlier phases of development.

74 **3. Legal basis**

75 This guideline should to be read in conjunction with the introduction and general principles (4) and part
76 III of the Annex I to Directive 2001/83 as amended.

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78 **4. Variability of immunogenicity of mAbs and its** 79 **consequences**

80 The factors discussed here are part of risk estimation in a risk-based approach of unwanted
81 immunogenicity.

82 The immunogenicity of mAbs is complex and there are a number of often poorly understood factors
83 which makes it difficult to predict with any certainty whether a therapeutically or diagnostically
84 administered monoclonal antibody is likely to provoke an immunogenic response. For heterologous e.g.
85 rodent sequence or human chimaeric mAbs, recognition of the antibody as being foreign is the primary
86 basis for antibody mediated immunity. In such situations, antibodies can be produced against various
87 epitopes present on different parts of the molecule e.g. anti-Fab, anti-Fc. Production of monoclonal
88 antibodies identical to the endogenous human amino acid sequence can reduce the risk of
89 immunogenicity but may not eliminate it because factors other than primary sequence contribute to
90 immunologic potential. In such cases, especially with humanised or human sequence mAbs the
91 immune response is predominantly anti-idiotypic (as the CDRs are unique in sequence for mAbs),
92 which clearly can compromise clinical responses to the mAb. In some cases, antibodies can be induced
93 against the constant region of human or humanised mAbs and this can affect the immunobiological
94 function of the mAb. There is less experience with clinical use of emerging constructs and these may
95 add to the perception of risk. Special consideration should be given to next generation products, for
96 example, bivalent mAbs.

97 The formulation, container system (including container closure systems), or storage conditions can
98 impact on the immunogenicity profile of the product. These factors may influence the immunogenic
99 properties by interactions of ingredients with the therapeutic protein and the container closure system
100 e.g. modification of protein conformation, extraction of impurities acting as immune adjuvants,
101 provoking alterations such as aggregation, particulates or deamidation . Altered glycosylation patterns
102 may decrease or enforce the immunogenic properties of the molecule, e.g. by shielding the protein
103 backbone or triggering innate immune responses by Toll-like receptors. Non-typical glycosylation
104 patterns, e.g. as may occur with entirely novel expression systems, may give rise to altered
105 immunogenicity compared to what is usually observed with more commonly used expression systems.
106 Other factors that contribute to immunogenicity include impurities arising from the production method,
107 route, dose and frequency of administration.

108 Patient related factors may influence immunogenicity e.g., differences in major histocompatibility and
109 human leukocyte antigen alleles among recipients and the physiological status of each patient. The
110 latter includes the individual history of previous microbial and viral infections. The rate of antibody
111 formation is also influenced by the individual immune responsiveness. Immunogenicity for mAbs can
112 be age related i.e. protein turnover is different in children compared to adults and this can result in
113 differences in observed immunogenicity, e.g. for antibodies used in treatment of juvenile arthritis
114 compared to rheumatoid arthritis at a comparable dose. Disease related factors also strongly influence
115 immunogenicity as does concomitant treatment. Furthermore, previous exposure to similar or related
116 monoclonal antibodies can also influence immunogenicity. Therapeutic antibodies used in a repeated
117 dosing scheme or with intermittent dosing scheme changes have a higher likelihood to induce
118 immunogenicity than single use mAbs.

119 Whether antibodies against a mAb have clinically significant effects depends on the binding site of the
120 antibody, the affinity of the antibody for the mAb and the titre of the antibodies that develop.
121 Antibodies against mAbs can transiently occur and then disappear during treatment or persist
122 throughout treatment or for longer. For some monoclonal antibody therapies, the development of
123 antibodies has no apparent adverse clinical consequences but for others it reduces efficacy or is
124 associated with therapy related adverse events.

125 **5. Approaches which may be helpful in predicting and** 126 **reducing the unwanted immunogenicity of mAbs.**

127 The design and selection of the mAb is the responsibility of the applicant. In-vitro approaches with the
128 aim of predicting immunogenicity have been developed (see general guidelines). In-silico modelling
129 may help to identify T-cell epitopes but does not predict whether immunogenicity will occur.
130 Confirmation/identification of T-cell epitopes using in-vitro cell based assays has been refined and is
131 often applied to therapeutic mAbs. The relatively large size of the mAb molecule makes it likely that
132 each molecule will contain several such epitopes. Both T-helper and T-regulatory epitopes have
133 apparently been identified on mAbs.

134 Various strategies for reducing the immunogenicity of mAb therapeutics are currently being
135 considered. These involve protocols for induction of tolerance to the mAb or 'de-immunizing' the mAb
136 by deletion of relevant T-cell epitopes. Deletion of T-helper epitopes may result in reduced
137 immunogenicity, whereas the reverse would be the case for deletion of T-regulatory epitopes.

138 **6. The clinical consequences of immunogenicity of mAbs**

139 The clinical consequences described following antibody development against mAbs include loss or
140 reduction of efficacy, local reactions, serum sickness/immune complex-mediated disease, and major
141 allergic reactions (e.g. urticaria, bronchospasm, bronchoconstriction). The severity of the consequences
142 of these different reactions can be affected by the underlying health status of the patient, e.g. a severe
143 IgE-mediated allergic reaction is more likely to result in serious consequences for a patient with chronic
144 asthma, and this potential reaction would be particularly serious if the patient was on home therapy.

145 It is important to note that not all induced antibodies are present in the serum i.e. they may be
146 present in various organs. It is important during the clinical development to measure antibody levels,
147 PK, PD markers, efficacy and safety simultaneously and over a period of repeated treatments. This
148 allows assessment of the clinical significance of antibody development, and also whether the antibody
149 effect changes over time, which could occur as a result of affinity maturation of the antibody response
150 or /and epitope spreading. Unexpected clinical observations (e.g., loss of efficacy or considerable
151 differences in PK) could be the result of undetected antibodies and should be further investigated.

152 Treatment with mAb can lead to the development of any class of immunoglobulin, although IgG is the
153 most commonly induced class. In some cases, low affinity IgM antibodies can be induced. Antibodies
154 can reduce the PK, PD and efficacy and can result in neutralisation of the mAb. The ability to measure
155 induced antibody in the serum is limited by the clearances of complexes. Formation of immune
156 complexes can lead to serum sickness which presents with features including haematuria, fever,
157 arthralgia and in severe cases acute renal failure.

158 In some instances, IgE testing needs to be considered for patients if the mAb contains non-human
159 carbohydrate structures. Another instance where development of IgE testing should be considered is
160 where the incidence of allergic reactions is high on first administration during early clinical

161 development of the product. The availability of an appropriate IgE assay allows exclusion of those
162 subjects with a positive result.

163 IgA antibody testing may only be needed on a case-by-case basis depending on the route of
164 administration but is not usually required. IgA antibodies induced by biological products have been
165 described and are usually accompanied by IgG antibodies. IgA antibodies are more likely to result from
166 airway/gut administration of the mAb and such antibodies are present in secretions. Detection of
167 mucosal immune responses using secreted fluids such as sputum as the sample is comparatively
168 insensitive due to interfering matrix effects. The testing strategy needs to take this into account.

169 In many cases, the incidence of immune response is too low to be fully identified during Phase III
170 clinical studies. Therefore systematic post-authorisation monitoring may be necessary and should be
171 adequately organised to capture clinical signs that could be related to immunogenicity. The
172 involvement of antibodies in this should be established by conducting appropriate assays.

173 Following marketing of mAbs, the features of major reactions such as serum sickness or severe allergic
174 reactions are diagnosed clinically. In cases where adverse events follow administration of the
175 implicated mAb, the reactions are attributed to an antibody response. The same rationale applies in
176 cases where loss of efficacy is observed. In view of the potential seriousness of unwanted
177 immunogenicity, it is important that confirmation and characterization of antibody induction is
178 conducted.

179 Because detection of antibodies against mAbs is rarely monitored in clinical practice, it is unclear –
180 other than in instances of obvious clinical evidence of one of the presentations listed above whether
181 the development of antibodies to mAbs has additional unrecognised consequences.

182 Detection of antibodies in low dose cohorts does not necessarily justify termination of treatment. The
183 need to terminate treatment because of antibody formation can only be assessed in combination with
184 clinical findings and requires careful assessment and monitoring.

185 **7. Problems experienced with screening and confirmatory** 186 **assays used in assessing immunogenicity of mAbs**

187 ***7.1. Assays for antibody detection***

188 The general guideline outlines relevant information on assays and strategies that apply to mAb
189 products. In principle, any immunoassay format can be used to measure antibodies against mAbs.
190 However, assays used to detect antibodies against mAbs are often more problematic and difficult than
191 those employed for other biologicals like G-CSF, EPO and interferons. Experience has shown that
192 measuring antibodies against antibodies can be technically very challenging. Many standard assay
193 formats involve the use of anti-immunoglobulin reagents such as antibodies against immunoglobulins,
194 protein A or protein G, but these are inappropriate for use in detecting antibodies against mAbs as they
195 very often bind to the product itself. Thus, for example simple ELISAs and radio-immunoprecipitation
196 assays are not usually suitable for use with mAbs unless they are adapted to overcome this problem.
197 Therefore, different assay approaches have to be adopted/developed. A common approach is to use
198 the 'bridging' ELISA format which does not require anti-immunoglobulin reagents and so can be
199 directly applied to studies with mAbs. However, this procedure may be less sensitive than other
200 immunoassay methods and can require significant development effort to produce a suitable assay. It
201 also will not efficiently detect the IgG₄ antibodies which can be produced in some cases. Another
202 approach is to use a Surface Plasmon Resonance (SPR) procedure. This does not require anti-
203 immunoglobulin reagents for detecting antibodies against mAbs. It is a real-time procedure and is
204 therefore fast and also detects rapidly dissociating antibodies which can be missed by other methods.

205 However, as SPR simply detects protein binding to the coated chip it needs to be confirmed that the
206 signal is caused by antibodies. It can be less sensitive than other methods for detecting high affinity
207 antibodies and, in the absence of automated sampling systems may have a low throughput.

208 Samples (normally serum or plasma) may contain substances that interfere with the assays which
209 produce false positive or negative results and/or incorrect assessment of antibody content. Well known
210 examples of this are complement components, mannose binding protein, Fc receptors, complement
211 receptor 1 and rheumatoid factors, but other substances can also cause problems. Assays often need
212 to be 'tailored' to reduce artefacts and achieve acceptable background signal levels, sensitivity and
213 specificity.

214 **7.2. Presence of mAb product in samples**

215 MAb products are usually administered in relatively high doses. They have relatively long half lives in
216 circulation and even fragments persist in blood for several days. This can cause significant problems in
217 detection of antibody responses due to the presence of mAb product in samples collected for antibody
218 assessment. This normally results in an artefactually low estimate of antibody content of affected
219 samples and can be so pronounced as to cause false negative results. Several approaches have been
220 proposed to overcome this problem. One possibility is to delay sampling until levels of mAb product
221 have declined sufficiently to no longer cause problems. This has been claimed to resolve the problem
222 with some mAb products, but requires careful assessment as it has the potential to fail to detect
223 immunogenicity, as induced antibodies have declined to undetectable levels by the time the samples
224 are taken. Another approach is to use methodology which is least affected by the problem. Some ECL
225 based immunoassays seem much less affected by residual product in samples than other methods,
226 including conventional bridging ELISAs. A commonly described procedure for dealing with the problem
227 is to include a preliminary antigen-antibody dissociation step in the assay design so that any
228 complexes present are disrupted before antibody is detected. Various versions of assays which include
229 acid incubations, sometimes coupled with affinity separation of product have been described for this. A
230 final possibility is to dilute samples so that residual product present is insufficient to interfere with the
231 assay. This approach needs care as it may result in a false negative assessment of immunogenicity if
232 the assay is not sufficiently sensitive to detect antibodies in the diluted samples. In some cases it may
233 be necessary to assay samples for the amount of residual mAb.

234 **7.3. Confirmatory Assays**

235 Confirmatory assays can suffer from the same problems as screening assays. It is important to select
236 an appropriate confirmatory assay taking account of the characteristics of the screening assay. The
237 most common approach for this is to include an incubation step with the mAb product in the assay to
238 show that this results in a significantly diminished signal when assaying real antibody positive samples.

239 **7.4. Controls**

240 Generation of positive control sera is in general a critical issue for immunogenicity studies for mAbs.
241 The chosen positive control serum affects sensitivity and specificity of the immunogenicity assay. If
242 human sera are not available (as is likely during early phases of product development) then use of
243 animal sera is the only option. Choice of species for this has important consequences. Non-human
244 primates produce primarily anti-CDR responses against human or humanized mAbs, which may closely
245 mimic human responses. However, non-primate species usually produce antibodies primarily against
246 the constant regions of the mAb, which is unlike human responses. Use of an anti-idiotypic antiserum
247 or mAb can, in some cases, provide a useful positive control. Selection of appropriate negative controls

248 is important. For confirmatory assays, spiking samples with an irrelevant mAb or (better) with a mAb
249 with the same Fc but different CDRs as the product can be used to confirm specificity.

250 **8. Assessing the neutralising capacity of antibodies induced** 251 **against mAbs.**

252 Antibodies which neutralize the biological activity of biological products may diminish clinical efficacy of
253 the product. It is normally expected that the neutralizing capacity of any antibodies induced is
254 measured. Deviations need to be justified. For most biological products, the most appropriate
255 neutralizing antibody assay is a bioassay which measures the neutralization of the bioactivity of the
256 product by antibodies. However, the nature of the clinical mode of action of mAbs implies that induced
257 antibodies which block mAb binding to target are those which are mostly associated with reduced
258 clinical efficacy. Therefore, competitive ligand binding assays are often the neutralizing assays of
259 choice for mAbs rather than classic bioassays. This distinguishes mAbs from other classes of biologicals
260 with regard to immunogenicity assessment.

261 MAbs exert their action by various mechanisms ranging from simple binding to antigen, which alone
262 mediates the clinical effect, to binding antigen and mediating one or more immunobiological
263 mechanisms which combine to produce the overall clinical response. Therefore, although simple
264 binding may seem to be the only mechanism operating to achieve clinical efficacy, other effects may
265 also play a role in this. In some cases multiple functions of the mAb may be involved in an additive or
266 synergistic manner to produce an overall combined clinical affect and this may be hard to dissect
267 experimentally to allow a clear understanding of how the mAb mediates its clinical potency. Therefore,
268 if intact mAbs are used, care must be taken not to assume that the Fc mediated immunobiological
269 effects of the product are not involved in clinical efficacy, even when simple antigen binding is
270 considered to be the primary mode of action. In such cases a thorough biological characterization of
271 the mAb must be undertaken, using appropriate biological and immunological assays. Following this,
272 the properties of the mAb need to be assessed to allow selection of an appropriate neutralizing assay
273 strategy.

274 **9. Risk-based Approach**

275 Every therapeutic mAb needs to be evaluated for immunogenicity individually and all immunogenicity
276 strategies should be adapted for each mAb development programme.

277 A risk-based approach can provide a starting point from which the further concept of immunogenicity
278 testing can be designed, but due to the diversity of risk factors, as discussed in this guideline, and the
279 variety of mAbs and mAb-related products, the recommendations given here cannot be generalized.
280 Assessment is based on the identification of risk factors inherent to the particular mAb in question, the
281 final drug product and the treated patient population. The mechanism of action and the basic structure
282 (chimaeric, humanized, fully human) are not sufficient for deciding on the attribution of risk level. For
283 a risk-based approach, applicants need to define what "risk" in this context means.

284 **9.1. Risk of mounting an unwanted immune response**

285 This will depend on various factors that can be divided into three different subgroups, i.e. product-,
286 process- and patient-related risk factors (see general immunogenicity guideline). These risk factors
287 should be identified, specified and comprehensively estimated. The relative significance of each factor
288 needs to be taken into account and comprehensively discussed individually for each product on a case-
289 by-case basis. Applicants should thoroughly justify their overall concept for the design and extent of
290 immunogenicity testing of their development programme, and should carefully plan this concept early

291 in product development. During development of a novel mAb, the overall assumed immunogenic risk
292 profile is composed of the total of all risk factors, whereas the most prominent factors usually
293 determine the extent of data necessary to allow for an assessment of immunogenicity. If, based on
294 such an evaluation, the risk of unwanted immunogenicity is perceived to be high, more safety
295 measures may have to be implemented in clinical trials to study immunogenic potential and measures
296 implemented to potentially handle the clinical consequences of these. For products that are claimed to
297 exhibit a particular advantage as regards immunogenic potential, (e.g. a claim in the Summary of
298 Product Characteristics) appropriate data is usually required to support such a claim.

299 MAbs are produced in various cell lines that can be of mammalian or non-mammalian origin. Non-
300 mammalian products may contain proteins acting as adjuvants which may lead to development of
301 antibodies thereby influencing the product's safety and efficacy. The same applies to other process
302 related impurities and these need to be reduced to the lowest levels possible during the purification
303 steps. In addition, product isoforms, as well as product related impurities and degradation products
304 should be considered in the risk assessment.

305 At the beginning of clinical development applicants may have to assign a high risk level, although the
306 mechanism of action may per se not necessarily suggest a higher risk. The risk level may, depending
307 on the results of larger clinical trials, need to be re-considered following the trials. This should be fully
308 justified by Applicants at the time of marketing authorisation.

309 Treatment modalities such as dosing, schedule of administration and concomitant treatments can
310 impact on the immunogenicity profile and should be carefully considered. The route of administration
311 can be classified as potentially lower (IV), medium (IM) or higher (SC) risk. For mAbs that are
312 developed as subcutaneous products, often intended for patient self-administration, the risk should be
313 carefully justified, taking into account that for such a clinical scenario, the mAb will, after initial
314 physician supervision, be administered by patients in a home setting with less physician surveillance.
315 In general, short-term treatment is usually associated with a lower risk of inducing an unwanted
316 immune response than long-term treatment. For the latter, the optimal time period between repeated
317 administrations should be determined.

318 Patient-related risk factors include age, genetic background and the underlying disease. Children may
319 have higher protein metabolism and a different immune status than adults, and cases are known
320 where data suggest a considerably higher immunogenicity of mAbs. In this patient group
321 immunogenicity should be evaluated separately as for adults. Extrapolation of immunogenicity data
322 from a previously conducted clinical study in adults is not sufficient. The genetic background or
323 underlying disease and concomitant therapy of the patient can influence its immune status impacting
324 on the immunogenicity of the product. The immune status of the patients should be taken into account
325 for risk estimation.

326 The risk perception may be higher if the methodology to either detect anti-drug antibodies or to detect
327 clinical consequences is not sensitive.

328 **9.2. The severity of clinical consequences of an immune response**

329 A pivotal aspect of risk assessment is the evaluation of clinical consequences of an unwanted immune
330 response. Therefore, the mode of action of the mAb (e.g., lytic, apoptotic), and especially the nature of
331 the target molecule (e.g., immunosilencing, immunostimulating), needs to be adequately characterized
332 and comprehensively investigated.

333 Antibody responses which target the idiotype of a mAb usually result in diminished efficacy. However,
334 it needs to be considered that based on the knowledge of the signalling cascade mediated by the mAb
335 target, a potential cross-reactivity of an anti-idiotypic immune response with certain agonistic

336 structures might be possible. Non-idiotypic antibodies to mAbs can be clinically important by positively
337 or negatively affecting the bioavailability of the product. Alternatively non-idiotypic antibodies against
338 mAb may react with endogenous serum immunoglobulins and trigger clinical effects similar to those
339 mediated by rheumatoid factors. Furthermore, the detection of binding, non-neutralizing antibodies
340 may be an early indication of the development of neutralizing antibodies due to epitope spreading.

341 Depending on the class and subclass of the mAb (which affects immunobiological functions e.g. binding
342 to Fc receptors) or the mechanism of action, individual mAb products may not all have the same risk
343 associated with an unwanted immune response. For example, mAbs can be neutralized by antibodies
344 resulting in a reduced efficacy, or result in adverse events such as infusion reactions. Such infusion
345 reactions can be severe, but can be potentially handled by appropriate clinical measures such as the
346 use of pre-medication. Antibodies can cross-link immunomodulatory mAbs with agonistic properties.
347 Such cross-linking can lead to enhanced activation of the immune system and potentially threatening
348 cytokine release syndromes, and maybe difficult to predict at the individual patient level. For agonistic
349 mAbs or for mAbs where cross-linking could on theoretical considerations lead to immunoactivation,
350 applicants should consider careful observation of patients in early clinical trials to see if such events
351 occur.

352 Another possible, though relatively rare, scenario is the occurrence of immediate hypersensitivity
353 reactions that usually appear after re-exposure to the mAb. The incidence of such unwanted immune
354 responses is also dependent on the time interval between doses and usually reduces with longer time
355 periods. Hypersensitivity reactions should be monitored and administration of high risk mAbs should be
356 conducted under conditions where life-threatening events can be mitigated. Close surveillance of
357 patients on the second and subsequent dosing with mAb is necessary, since sensitization can occur de-
358 novo upon first exposure.

359 **9.3. Consequences with regard to different risk classes**

360 For all mAbs a validated screening and confirmatory assay should be performed followed by a validated
361 neutralizing assay in case of positive results in the confirmatory assay. Distinguishing between
362 neutralizing and non-neutralizing antibodies is essential for all mAbs regardless of their risk level as
363 lack of, or even reduced efficacy due to the neutralizing activity of the antibodies may result in a
364 discontinuation of treatment with the mAb.

365 Correlation of antibody development with clinical outcome is important and has to be thoroughly
366 evaluated. However, the frequency of sampling and analysis could vary depending on the individual
367 risk level. Depending on the risk level attributed to a mAb it may be possible to reduce sampling
368 frequency in later stages of development, provided that no adverse events or reduced efficacy is
369 observed. Nevertheless, banking of samples should be undertaken on a routine basis over the whole
370 development programme. For high risk mAbs sampling should be frequent during the whole clinical
371 development. In this situation it is advisable to analyze samples in real time.

372 The approach outlined above should enable appropriate immunogenicity testing and assessment of
373 mAbs on the basis of scientific data underpinning identified immunogenicity risks. It is recommended
374 that the applicants address these risks adequately in a Risk Management Plan (RMP) ensuring not only
375 risk identification and characterisation but also risk monitoring, minimization and mitigation strategies.

376 **References**

377 • Directive 2001/83/EC, as amended.

378 • Part III of the Annex I of Directive 2001/83/EC, as amended.

379 • Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins
380 (EMA/CHMP/BMWP/14327/2006)