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4 Revised guideline on safety and residue data
5 requirements for pharmaceutical veterinary medicinal
6 products intended for minor use or minor species
7 (MUMS)/limited market
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9
10 This guideline updates the CVMP Guideline on safety and residue data requirements for veterinary
11 medicinal products intended for minor uses or minor species/ limited market
12 ([EMA/CVMP/SWP/66781/2005-Rev.1](#)).

13
14 Comments should be provided using this [template](#). The completed comments form should be sent
to vet-guidelines@ema.europa.eu

15
16 **Keywords** Minor use, minor species, safety data, residue data, veterinary medicinal
products



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71 **Executive summary**

72 In order to stimulate the research, development and innovation of new veterinary medicines intended
73 for minor uses or minor species (MUMS)/limited market the CVMP developed guidelines on data
74 requirements for MUMS/limited market veterinary medicinal products for quality, safety and efficacy
75 for pharmaceuticals and a guideline for immunologicals. These guidelines are intended to reduce data
76 requirements where possible for products classified as MUMS/limited market while still providing
77 assurance of appropriate quality, safety and efficacy and complying with the legislation in place and
78 leading to an overall positive benefit-risk balance for the product.

79 These MUMS guidelines have now been reviewed and revised with the aim of updating the acceptable
80 data requirements in light of experience gained and clarifying, where appropriate, the applicability of
81 the MUMS data requirements. This guideline describes the data requirements regarding safety and
82 residues for pharmaceutical veterinary medicinal products, and MRL application falling within the scope
83 of MUMS/limited market. With regards to the safety data requirements the key consideration is
84 whether the veterinary medicine is intended for treatment of a minor species rather than whether is
85 designated as 'minor use' or 'limited market'.

86 This guideline also presents several opportunities to waive animal testing requirements for veterinary
87 medicines intended for MUMS/limited market, which is in line with the recent implementation of
88 Directive 2010/63/EC (regarding the protection of animals used for experimental and other scientific
89 purposes) and the 3Rs principles of replacement, reduction and refinement.

90 This update introduces the extrapolation criteria to be considered by the CVMP when assessing
91 applications for MRLs, and refers to Commission Regulation (EU) 2017/880 of 23 May 2017 laying
92 down rules on the use of a maximum residue limit established for a pharmacologically active substance
93 in a particular foodstuff for another foodstuff derived from the same species and a maximum residue
94 limit established for a pharmacologically active substance in one or more species for other species, in
95 accordance with Regulation (EC) No 470/2009 of the European Parliament and of the Council (5).

96 These updated criteria should enable applicants to provide the minimum required data to increase the
97 availability of medicines for both major and minor species, by allowing the CVMP to set MRLs for
98 additional animal species and commodities.

99 **1. Introduction**

100 For some time there has been considerable concern amongst all parties concerned with animal health
101 in the EU about the lack of authorised veterinary medicinal products for minor uses and for minor
102 species. The availability of safe and effective veterinary medicinal products for minor uses or minor
103 species (MUMS)/limited market will improve both animal welfare, animal health and, in some cases,
104 public health. The Agency at the behest of its Management Board began discussions and consultations
105 on this increasing problem in 1998 and, since that time, the CVMP has worked on the matter and is
106 active in initiatives to address the problem of lack of veterinary medicines.

107 One of the initial measures introduced by the CVMP was to review data requirements for veterinary
108 medicinal products intended for MUMS, both for pharmaceuticals and immunologicals, and, if possible,
109 to establish standards for demonstration of quality, safety and efficacy for these. A set of CVMP
110 guidelines on data requirements for veterinary medicinal products intended for minor use minor
111 species were finalised in 2006 to 2008 (EMA/CVMP/QWP/128710/2004,
112 EMA/CVMP/SWP/66781/2005, EMA/CVMP/EWP/117899/2004, EMA/CVMP/IWP/123243/2006).

113 Since then the Agency Policy for classification and incentives for veterinary medicinal products
114 indicated for MUMS/limited markets was established and implemented on 1 September 2009 and
115 updated in December 2014 (EMA/308411/2014). The policy is supported by a guidance document on
116 the classification of veterinary medicinal products indicated for minor use minor species (MUMS) /
117 limited market (EMA/CVMP/388694/2014) providing guidance for implementing the policy and the
118 procedure and criteria for classification of products or applications as MUMS/limited market.

119 The policy is intended to stimulate the development of new veterinary medicines for minor species and
120 for diseases occurring infrequently or in limited geographical areas in major species that would
121 otherwise not be developed in the current market conditions. The guidelines on data requirements for
122 products classified as MUMS/limited market are an integral part of the policy.

123 These guidelines are intended to reduce data requirements where possible for products classified as
124 MUMS/limited market while still providing assurance of appropriate quality safety and efficacy and
125 complying with the legislation in place and leading to an overall positive benefit-risk balance for the
126 product.

127 In addition, the reduced data requirements for MUMS has the potential to reduce the numbers of
128 animals used in testing, which is in line with the principles of the 3Rs (reduce, refine, replace), in line
129 with Directive 2010/63.

130 These guidelines have now been reviewed and revised with the aim of updating the acceptable data
131 requirements in light of experience gained and clarifying, where appropriate, the applicability of the
132 MUMS data requirements.

133 It is the intention to provide clear guidance under which circumstances data requirements can be
134 reduced for MUMS/limited market products to facilitate the applicant's work for estimating the required
135 resources for a MUMS/limited market application and preparing the application dossier and provide for
136 predictability. However, it is recognised that this is not always feasible as not all possible scenarios can
137 be addressed in a general guidance document.

138 Furthermore, the specific requirements will depend on the data and knowledge available, e.g. there
139 may be scope for data reductions if a product has already been authorised for a major species, an MRL
140 has been established for another species, or if a product contains an active substance belonging to a
141 well-known class of substances. However, for products containing entirely new active substances,
142 novel therapy products or products representing first in class, the possibilities for data reduction are
143 likely to be limited. Similarly, for products presenting a specific risk, e.g. for products containing an
144 antimicrobial or vaccines containing genetically modified organisms (GMOs), the possibility for reducing
145 data requirements will be severely limited in the area related to addressing the risk, i.e. adequate data
146 to justify the indication and establish the appropriate dosage regimen or data to ensure safe and
147 efficacious use of such a vaccine will need to be established, even if the product is classified as
148 MUMS/limited market.

149 The general aim of this guideline is to define acceptable data requirements for safety and residues
150 documentation for veterinary medicinal products intended for minor uses or minor species. In this
151 context, data requirements for the demonstration of safety will be influenced to a certain extent by the
152 active substance/product type and whether or not the product is/has been authorised in a related
153 major species for the same or a similar route of administration. It follows that where an active
154 substance/product is or has been authorised for the same or a similar route of administration in a
155 major species, information relating to use in that species may be used in support of the application
156 and, where justified, this may obviate the need for certain toxicity studies. For novel active substances
157 and for those where limited information is available relating to their use in any animal species,
158 comprehensive toxicity information will be required. In accordance with the provisions of the European

159 Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific
160 Purposes and Directive 2010/63/EU on protection of animals used for scientific purposes, the 3R
161 principles (replacement, reduction and refinement) should be applied to in regulatory testing of
162 pharmaceuticals.

163 The guidance provided in this document is general. Applicants are advised to request scientific advice
164 on their individual data package to confirm the precise requirements for their specific application.

165 **2. Scope**

166 The objective of this guideline is to clarify the requirements as follows:

- 167 • The data requirements for minor species for a Maximum Residues Limit (MRL) application with no
168 MRL established for other species.
- 169 • The data requirements for minor species for an MRL application where an MRL has been
170 established for other species.
- 171 • The data requirements for a marketing authorisation application for a minor food producing
172 species.
- 173 • The data requirements for a marketing authorisation application for a minor non-food producing
174 species.

175 As a general principle, the CVMP and VICH guidelines concerning safety and residues are applicable to
176 minor use/minor species products.

177 **3. Definitions**

178 Definitions are provided in the revised policy for classification and incentives for veterinary medicinal
179 products indicated for minor use minor species (MUMS)/limited market (EMA/308411/2014).

180 Minor species: There is no legislative definition in the EU for major or minor species.

181 Major species have been defined by the CVMP as follows:

182 Major food-producing species:

- 183 – cattle (dairy and meat animals);
- 184 – sheep (meat animals);
- 185 – pigs;
- 186 – chickens (including laying hens);
- 187 – salmon¹.

188 Major companion animal species:

- 189 – cats;
- 190 – dogs.

191 All other animal species, which are not considered major, are as a consequence, by default, classed as
192 minor species.

¹ Salmon should be considered a major species, however other species of the *Salmonidae* family such as rainbow trout should be considered minor species. The term salmon is understood in this context as Atlantic salmon (*Salmo salar*).

193 Minor use: Minor use in a major species is generally considered as the use of veterinary medicinal
194 products for the treatment of diseases that occur infrequently or occur in limited geographical areas
195 and thus are indicated for a smaller market sector.

196 Limited market: A market for a veterinary medicinal product that is limited in size due to the product
197 being indicated for a disease or condition that represents a minor use in a major species or that occurs
198 in a minor species.

199 Legal basis

200 **4. Legal basis**

201 Regulation (EC) No 470/2009 lays down Union procedures for the establishment of residue limits of
202 pharmacologically active substances in foodstuffs of animal origin. This Regulation replaced Council
203 Regulation (EEC) No 2377/90 and the Annexes that contained the list of allowed and non-allowed
204 substances were entered into a new Commission Regulation (EU) No 37/2010 of 22 December 2009.
205 The information required for the establishment of MRLs by the European Union is set out in
206 Commission Regulation (EU) 2018/782 establishing the methodological principles for the risk
207 assessment and risk management recommendations referred to in Regulation 470/2009 (6).

208 Requirements for safety testing for a marketing authorisation application are laid down in Article 12 of
209 Directive 2001/82/EC, and are specified in Annex I of Directive 2001/82/EC, Title I for
210 pharmaceuticals, as amended by Directive 2009/9/EC.

211 One of the intentions of the legislation in place for the authorisation of veterinary medicines as laid
212 down in the preamble of Directive 2001/82/EC, preamble point Nos. 9 and 10 of Directive 2004/28/EC,
213 is to facilitate the authorisation of certain veterinary medicinal products:

214 '(9) The costs of research and development to meet increased requirements as regards the quality,
215 safety and efficacy of veterinary medicinal products are leading to a gradual reduction in the range of
216 products authorised for the species and indications representing smaller market sectors.'

217 '(10) The provisions of Directive 2001/82/EC also need, therefore, to be adapted to the specific
218 features of the sector, particularly to meet the health and welfare needs of food-producing animals on
219 terms that guarantee a high level of consumer protection, and in a context that provides adequate
220 economic interest for the veterinary medicinal products industry.'

221 This is also reflected in Annex I of Directive 2001/82/EC under Introduction and General Principles.

222 '(10) In cases of applications for marketing authorisations for veterinary medicinal products indicated
223 for animal species and indications representing smaller market sectors, a more flexible approach may
224 be applicable. In such cases, relevant scientific guidelines and/or scientific advice should be taken into
225 account.'

226 **5. MRL Applications for minor species with no MRL** 227 **established for other species – General requirements**

228 **5.1. Safety data requirements**

229 Food derived from a minor species usually constitutes a small proportion of the diet of the average
230 European consumer. It may, nevertheless, constitute a major portion of the intake of animal derived
231 products in certain geographic areas or for certain subpopulations and therefore consumer safety must
232 not be compromised.

233 It was concluded that the standard safety data requirements relating to any effects that might occur
234 after single and repeated exposure could not be reduced for minor species.

235 **5.1.1. Establishment of the ADI and MRL in a minor species**

236 Table 1. presents the data requirements for testing the safety (i.e. pharmacology and toxicology) of
237 those substances that are used in minor food-producing species and for the establishment of an MRL,
238 where MRLs have not been established for use in a major food-producing species. It should be noted
239 that for the safety evaluation, the data requirements are broadly the same as for major species.

240 **5.1.2. Pharmacological data**

241 Pharmacological data must provide sufficient information for an assessment of the pharmacodynamic
242 effects (i.e. primary and secondary pharmacodynamics) in order to establish whether a
243 pharmacological 'acceptable daily intake' (ADI) is required. Pharmacological studies may assist in the
244 understanding of toxicological phenomena or show pharmacological effects in the absence of
245 toxicological responses. Thus, if there are no human data, details of pharmacodynamic studies in
246 laboratory animals are required. However, an abbreviated dataset not including pharmacodynamic
247 studies may be considered, depending on the substance under consideration, but the absence of data
248 must be scientifically justified with a summary of anticipated pharmacodynamic effects.

249 Pharmacokinetic studies in laboratory animals, and if available, human data should be submitted for
250 the assessment of the fate of the substance. These are fundamental data that are required for
251 selection of appropriate species for toxicity studies and the establishment of an ADI and MRLs.

252 **5.1.3. Toxicological data**

253 Toxicological data are required for an assessment of adverse effects and to establish a toxicological
254 ADI and the dataset must be sufficient to establish this. CVMP/VICH guidelines should be followed with
255 regard to the choice of the studies required by this guideline and the toxicological tests themselves
256 should be conducted in accordance with the relevant OECD or other internationally recognised
257 guidelines. Any deviation should be adequately justified.

258 **5.2. Residue data requirements**

259 **5.2.1. Total residue studies**

260 Total residue (radiolabelled) studies will normally be required for most veterinary substances to
261 identify the residue of concern in the minor species and to establish the ratio of the marker residue(s)
262 to total residues, if necessary. Possible exemptions are substances where there is evidence that the
263 only residues of concern are known and can be determined by validated analytical methods (e.g.
264 pharmacologically or microbiologically active component in case of pharmacological/microbiological
265 ADI). For a novel compound intended for minor species, the requirement for a radiolabelled study
266 could be waived on a case-by-case basis upon request when scientifically justified and supported by
267 substitute data. The applicant could request the CVMP to give scientific advice on this issue before the
268 application is submitted to EMA. The advice of the CVMP may be based on the following considerations:

269 i. available absorption, distribution, metabolism and excretion (ADME) data (e.g. in laboratory
270 species) that may be extrapolated to the minor species.

271 ii. if the novel compound belongs to a class of (veterinary or human) medicines of which it has
272 been shown, in ADME studies in laboratory animals or other target species, that one or more of
273 the following apply:

274 • such medicines are not or are hardly metabolised,

275 • the metabolism of such medicines is well known and comparable (within the chemical class
276 and across species),

277 • structural differences between the novel compound and other substances of the same class
278 of drugs are not indicative for a significantly different metabolism,

279 and:

280 • there is no indication of metabolites or degradation products of specific concern,

281 • the parent compound of such medicines can be considered as a suitable marker residue for
282 surveillance,

283 • the information on the metabolism of such medicines provides an estimate of the ratio of
284 marker to total residues, which can be used, for the calculation of the intake of residues
285 resulting from the proposed MRLs.

286 There are two other exemptions from the rule. As detailed in the Note for guidance on the
287 establishment of MRL for Salmonidae and other fin fish (EMA/CVMP/153b/97 FINAL), in fish the
288 parent compound is normally acceptable as a valid marker residue and radiolabelled studies are not
289 required. Radiolabelled studies are also not required to establish an MRL for a substance in honey.

290 **5.2.2. Marker Residue Studies**

291 Where MRLs need to be established in the minor species, marker residue depletion studies in
292 accordance with the requirements of Commission Regulation (EU) 2018/782 should be submitted.

293 **5.2.3. Regulatory Analytical Methods**

294 For the purposes of monitoring residues, there is also a need for a regulatory analytical method for
295 minor species. However, a reduced validation of the proposed regulatory analytical method could be
296 acceptable. The method should be validated in respect of the limit of quantification (LOQ) and, at least,
297 for accuracy and precision at the level of the MRL and half the MRL. With regard to specificity, possible
298 interference from matrix components and from chemically closely-related substances used in
299 veterinary therapy should be investigated. Adequate storage and sample processing stability data
300 should also be supplied.

301 **5.3. Establishment of MRLs for honey**

302 The establishment of MRLs in honey requires residue studies. While the determination of a theoretical
303 safe level in honey could, in principle, be calculated directly from the ADI or the portion of the ADI
304 available, an MRL cannot be set without knowing the residue concentrations that would typically occur
305 in practice. Current requirements for residue studies in honey are given in Commission Regulation (EU)
306 2018/782 and in VICH GL56.

307 Assessment of residues in honey is more complex than in mammalian or avian tissues. In honey, there
308 is no time dependent depletion/elimination of residues as a result of pharmacokinetics (as in
309 mammalian/avian tissues). Residues, once present in honey, largely remain there. Apart from possible

310 chemical degradation of a substance in honey matrix over time, the main variable responsible for the
311 level of residues at harvest time is the honey yield (dilution effect), which in large part depends on the
312 production site (geographical area) and weather conditions at flowering time. These variables are
313 unpredictable and not directly related to a specifiable period of time. Therefore, the only feasible
314 withdrawal period in honey is a 'zero' withdrawal period. Residue studies covering a reasonable range
315 of commercial treatment conditions are needed to support this 'zero' withdrawal period. These studies
316 should show that there are no non-conforming residues (i.e. above the MRL) under conditions of good
317 bee keeping practice.

318 **6. MRL Applications for minor species where MRLs have been** 319 **established for other species – General requirements**

320 ***6.1. Safety data requirements***

321 For substances where MRLs have already been established for other species, the safety data must have
322 been submitted and evaluated in order for a reduced data set to be considered when establishing MRLs
323 in minor species. The outcome of the previous evaluation could have resulted in the establishment of
324 an ADI and subsequently MRLs. It is also possible that no ADI was established, resulting in a 'no MRL
325 required' entry in Regulation 37/2010. These substances are normally considered as safe, but the 'no
326 MRL required' entry could be restricted to a particular route of administration, or have been intended
327 only for minor species, and previous 'rules' had been applied, resulting in a reduced data requirement
328 for the safety package. In such instances, safety data may be required, depending on the application
329 submitted.

330 **6.1.1. Establishment of the ADI and MRL in a minor species**

331 For substances where the ADI has already been established, no additional safety data are required.
332 The ADI that has already been determined can be used to establish MRLs in the minor species,
333 together with the relevant residue data.

334 In situations where no ADI has been determined for a substance but with a 'no MRL required' entry for
335 other species, possibly with a restriction (e.g., For topical use only), if the MRL that has been sought is
336 without any restriction, then safety data as set out in section 5 above will be required.

337 ***6.2. Residue data requirements***

338 Once the need for the establishment of MRLs for the minor species has been identified, the first point
339 to consider is whether extrapolation of MRLs established in other species to the minor species is
340 possible. The criteria for extrapolation are set out in 6.2.1 below. If extrapolation is not possible, then
341 residue data as set out in section 5.2 above are required.

342 **6.2.1. Extrapolation of MRLs from major to minor species**

343 Previously, much effort by the CVMP regarding availability of veterinary medicines focussed on
344 extrapolation of existing MRLs from major species to minor species and significant progress has been
345 made in this area; guidance has been developed (CVMP Note for Guidance on the Establishment of
346 Maximum Residue Limits for Minor Animal Species, EMEA/CVMP/153a/97 and Note for Guidance on the
347 Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin,
348 EMEA/CVMP/187/00-FINAL). The principle of extrapolation received legal backing when it was
349 incorporated in Article 5 of Regulation (EC) 470/2009. The CVMP now actively considers whether

350 extrapolation would be possible to other species and food commodities as part of its MRL evaluations,
351 in line with Commission Regulation 2017/880, laying down rules on the use of a maximum residue limit
352 established for a pharmacologically active substance in a particular foodstuff for another foodstuff
353 derived from the same species and a maximum residue limit established for a pharmacologically active
354 substance in one or more species for other species, in accordance with Regulation (EC) No 470/2009 of
355 the European Parliament and of the Council.

356 Regulation 2017/880 sets out the considerations that the CVMP will undertake for all new MRL
357 applications in terms of potential extrapolation opportunities. Included in this are the minimum criteria
358 for extrapolation, which may not be met in all cases, but could be met with minimal additional data
359 where these are available. It should be noted that the potential extrapolation opportunities have been
360 considerably increased by adoption of this regulation. Applicants are invited to actively consider these
361 opportunities when applying for MRLs.

362 **7. Marketing authorisation applications for food producing** 363 **minor species – General requirements**

364 **7.1. Safety data requirements**

365 The requirements for Marketing Authorisations for food producing species as given in the Directive
366 2001/82/EC as amended and the CVMP/VICH Safety guidelines were considered and reductions in the
367 safety data requirements have been identified.

368 **7.1.1. Tabulated minimum datasets**

369 Table 2. presents the data requirements for safety testing (i.e., pharmacology and toxicology) for a
370 Marketing Authorisation for minor food producing species where there are MRLs established for the
371 active ingredients, in accordance with Part 3A Safety Testing as laid down in Annex I of Directive
372 2001/82/EC, as amended by Directive 2009/9/EC. As substances with MRLs are likely to have a
373 published Summary Report (SR) or European Public MRL Assessment Report (EPMAR), information
374 from these publications may be used in support of the pharmacology and toxicology part of the
375 application dossier.

376 **7.1.2. Marketing Authorisation applications and the use of MRL summary** 377 **report or EPMARs in accordance with Directive 2001/82/EC, as amended**

378 It should be noted that Directive 2001/82/EC, as amended, permits Marketing Authorisation
379 applications made in accordance with Article 13a, to submit the published EMA/CVMP SR/EPMAR as
380 published literature, particularly for the safety tests, thus allowing an exemption for pharmacological
381 and toxicological data. Article 13a refers to applications made on the basis of 'well-established use' and
382 permits the submission of 'appropriate scientific literature' in place of study data. Therefore, when an
383 MRL has been established for a substance for a major or minor food producing species, it will be
384 possible for the Marketing Authorisation applicant to submit the EMA/CVMP MRL SR/EPMAR as part of
385 the published literature submitted. These data can also be used for MAAs intended for non-food species
386 (see section 8.1.2), if available.

387 **7.1.3. Pharmacological data**

388 Pharmacological studies in laboratory animals (Part 3.A of the dossier) and the target species
389 (Part 3.B) can be replaced by cross reference to the target species studies submitted in Part 4 of the

390 dossier, by means of a summary of any observed effects in the pharmacodynamics studies and a
391 summary of the pharmacokinetics data to include absorption, distribution, metabolism and excretion
392 (ADME). The pharmacokinetics of the active substance following oral exposure to residues will have
393 been considered as part of the MRL application and cross reference can be made to the EMA/CVMP MRL
394 SR/EPMAR.

395 **7.1.4. Toxicological data**

396 Where there is no MRL SR or EPMAR available, toxicological data are required for the evaluation of user
397 safety and the assessment of adverse effects. For example, the data set must be adequate for the
398 evaluation of possible adverse effects on fertility or reproduction. It should also consider potential
399 problems associated with administration, such as exposure by inhalation or dermal contact and
400 accidental self-injection. The omission of studies should be adequately justified.

401 Where available, CVMP/VICH guidelines should be followed and the toxicological tests themselves
402 should be conducted in accordance with the relevant OECD guidelines or other internationally
403 recognised guidelines and any deviation should be justified. The toxicology of the active substance
404 following oral exposure to residues will have been considered as part of the MRL application and cross
405 reference can also be made to the EMA/CVMP MRL SR/EPMAR. See the user safety section below for
406 further guidance.

407 **7.1.5. User safety assessment**

408 A user risk assessment, considering the administration of the product, and risk management proposals
409 must be submitted for all applications. The requirements of the user safety guideline
410 (EMA/CVMP/543/03-Rev.1) should be applied. This guideline allows for consideration of (low)
411 exposure frequencies. This assessment should include a discussion of the effects found in the
412 pharmacological and toxicological data and relate this to the type and extent of human exposure to the
413 product with a view to formulating appropriate user warnings.

414 **7.1.6. Environmental safety**

415 Environmental safety requirements for minor species and minor use are described in the questions 4
416 and 5, respectively, of the CVMP/VICH Phase I guidance as given in CVMP/VICH/592/98-FINAL. This
417 guideline came into force in July 2000, and in view of the modification of the legislation since then, the
418 following is to be considered for minor species:

419 An environmental risk assessment (ERA) for minor species is not required in the case where an ERA is
420 available for a major species, provided that: 1) the minor species is reared under similar conditions as
421 the major species, and the primary environmental release of the VMP used for minor and major species
422 is to the same environmental compartment, e.g., soil or water²; 2) the exposure to the same
423 environmental compartment from the use of the minor species is not higher than from the use in the
424 major species, and the total dose administered to the minor species is no greater than used in the
425 major species; 3) any risks identified in the major species are also considered in the ERA for the minor
426 species; and, 4) the ERA of the major species belongs to the same applicant. In that case the ERA
427 conclusions from the major species also apply to the minor species.

² If a VMP for a major species, for example, is approved for stabled husbandry, with manure as the primary environmental entry point, the applicant for the same VMP used for a minor species in aquaculture would need to undertake an ERA.

428 **7.2. Residue data requirements**

429 **7.2.1. Withdrawal periods for minor species**

430 Whereas the MRL refers to the active chemical substance itself, the withdrawal period refers to, and is
431 dependent on, the specific marketing formulation and dosing regimen (highest dose and longest
432 duration indicated for a particular species) of a veterinary medicinal product (VMP). Each product has
433 to be considered on its own merits. Current guidelines on setting withdrawal periods do not
434 differentiate between minor and major species. Data requirements are practically the same (see Table
435 4.) except in some of the following cases.

436 Current requirements for residue studies in honey are given in VICH GL56. Draft guidance on residue
437 studies in aquatic species (VICH GL57) is also available.

438 **7.2.1.1. Identical products**

439 In case of the same VMP where the active substance has the same MRL in the major/minor species,
440 following an approach similar to the approach for extrapolation of MRLs could be considered, i.e. no
441 residue depletion studies may be required in the minor species. In accordance with the approach
442 accepted for extrapolation of MRLs, an extrapolation of withdrawal periods should be possible from
443 cattle/sheep to other ruminants, from chickens to other avian species, from Salmonidae to other fin
444 fish, etc. Exemptions are products having a potential to leave local residues (in particular injectable
445 products administered intramuscularly and/or subcutaneously as well as dermal/intramammary
446 applications). In this case, information on the behaviour of residues at the site of administration needs
447 to be assessed before the withdrawal period is extrapolated; limited residue depletion studies (e.g., at
448 2 time points, one just before the reference withdrawal period and one after it) or alternatively, an
449 uncertainty (safety) factor, to compensate for uncertainties in the extrapolation, could be considered
450 (multiplication of the withdrawal period in the major species by an uncertainty factor of 1.5). Use of an
451 uncertainty factor would only be appropriate if the dose and volume of injection are no greater than
452 that administered in the major species.

453 **7.2.1.2. Products with identical active ingredient but with different formulation/different**
454 **dosing regimen/routes of administration**

455 Differences in the pharmaceutical composition can have a considerable impact on pharmacokinetic
456 properties and route-to-route or dose-to-dose extrapolations of withdrawal periods might not be
457 feasible, particularly if injectable formulations are involved. With respect to non-identical products, a
458 more cautious approach is necessary and products need to be assessed on a case-by-case basis.

459 In the case of a multiple administrations of a product, it would be important to know the accumulation
460 profile of the active substance or the marker residue in the minor species. Normally, some
461 experimental information in the minor species will be required to support the withdrawal period. An
462 approach based on limited residue data could be acceptable: pharmacokinetic studies demonstrating
463 similar profiles could provide useful data to support an extrapolation of withdrawal periods between
464 major/minor species. Setting of a withdrawal period in the minor species based on overall
465 pharmacokinetic parameters (e.g., plasma terminal elimination half-life) could be an option for certain
466 compounds (e.g., compounds distributed mainly in extracellular fluids/plasma only).

467 In the absence of residue data, use of an uncertainty (safety) factor to compensate for uncertainties in
468 the extrapolation could be considered (multiplication of the withdrawal period in the major species by a
469 certain factor, e.g., 1.5) if it is clear that the new formulation is qualitatively and quantitatively similar

470 to the original formulation and is used at or below the dose used for the original formulation with the
471 same route of administration.

472 When the product for the minor species is to be used at a significantly higher dose level/dosing
473 regimen, conventional residue studies will be required to confirm the withdrawal period. Where the
474 product for the minor species is intended for injection (intramuscular or subcutaneous), residue data
475 from the injection site will also be needed. Likewise, for veterinary medicinal products for topical
476 applications, local residues in edible tissues below the site of administration need to be investigated.

477 For residue studies in the minor species the analytical method used in a residue depletion study must
478 be validated in line with VICH GL49 (EMA/CVMP/VICH/463202/2009) otherwise the study itself would
479 not be valid (see below at 7.2.1.4 and also Table 5.).

480 **7.2.1.3. Products not authorised previously for major species**

481 Residue studies according to guidelines are normally required for veterinary medicinal products for a
482 minor species where previously no similar product was authorised for a major species.

483 Extrapolation may be possible if a residue study is available for a minor species in the same category
484 conducted and evaluated according to the guidelines (e.g., turkeys to ducks) (Pharmacokinetic
485 parameters should be comparable, pharmaceutical form, route of administration and dosing regimen
486 should also be the same).

487 **7.2.1.4. Analytical methods (in residue studies supporting withdrawal periods in minor 488 species)**

489 The analytical method used in a residue depletion study must be validated in line with VICH GL49
490 (EMA/CVMP/VICH/463202/2009) otherwise the study itself would not be valid. See Table 5.

491 **7.2.1.5. Withdrawal periods for compounds with a 'no MRL required' entry**

492 Many compounds with a 'no MRL required' entry have been placed there based on consideration of
493 quick metabolism/elimination of residues and/or limited use (see Annex II criteria in the CVMP Note for
494 Guidance on the Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of
495 Animal Origin [EMA/CVMP/187/00-FINAL] Appendix 1). For such compounds, no MRL is available on
496 which to base the withdrawal period. For many compounds with a 'no MRL required' entry there is an
497 established ADI, but there are several compounds for which there is none (e.g., xylazine,
498 levomethadone). For compounds with an ADI, the ADI can serve as a reference point for the
499 withdrawal period. A complication inherent in the ADI approach is that the ADI often relates to total
500 drug derived residues or a combination parent compounds plus metabolites. Consequently, in a strict
501 sense, a withdrawal period based on the ADI would necessitate residue studies for more than a single
502 component, i.e. normally total residue (radiolabelled) studies, which are extremely complex and costly.
503 A request for total residue (radiolabelled) studies for setting withdrawal periods is normally not
504 reasonable or warranted for compounds fulfilling a 'no MRL required' criteria. In this case, it would be
505 sufficient to estimate a withdrawal period based on depletion data for the most relevant residue
506 component in the tissue with the slowest depletion rate (could be the parent compound and/or major
507 metabolite). Supporting information allowing the estimation of food basket residues should be available
508 from the MRL procedure (residue distribution data between tissues, ratios between residue
509 components in tissues). The same consideration applies to compounds with no ADI where an
510 alternative exposure limit (e.g., Tolerable Dietary Intake) may serve as reference point for the
511 withdrawal period.

512 Withdrawal periods for compounds with a 'no MRL required' entry for which an ADI has been set, it
513 would be reasonable to use an uncertainty factor (e.g., 1.5) for extrapolating the withdrawal period for
514 minor species from major species.

515 **8. Marketing authorisation applications for non-food** 516 **producing minor species – General requirements**

517 **8.1. Safety data requirements**

518 The requirements for Marketing Authorisations for non-food producing species, as given in Annex I to
519 Directive 2001/82/EC as amended by Annex I to Directive 2009/9/EC, already foresees exemptions for
520 non-food producing species; therefore, very limited reductions in data requirements were identified
521 when considering minor species. The specific safety data requirements are listed in Table 3.

522 **8.1.1. Tabulated minimum datasets**

523 Table 3. presents the data requirements for safety testing (i.e., pharmacology and toxicology) for a
524 Marketing Authorisation for non-food-producing species, in accordance with Part 3A Safety Testing as
525 laid down in Annex I Directive 2001/82/EC as amended by Directive 2004/28/EC, with the exception of
526 environmental safety requirements, and in accordance with the CVMP/VICH Safety guidelines.

527 **8.1.2. Marketing Authorisation applications and the use of MRL SR or** 528 **EPMARs in accordance with Directive 2001/82/EC, as amended**

529 It should be noted that the amending Directive 2004/28/EC permits Marketing Authorisation
530 applications made in accordance with Article 13a, to submit the published EMEA/CVMP MRL SR/EPMAR
531 as published literature, particularly for the safety tests, thus allowing an exemption for
532 pharmacological and toxicological data. Article 13a refers to applications made on the basis of
533 'well-established use' and permits the submission of scientific literature in place of study data.
534 Therefore, when an MRL has been established for a substance for a major or minor food producing
535 species, it will be possible for the Marketing Authorisation applicant to submit the EMEA/CVMP MRL SR
536 or EPMAR as part of the published literature submitted. Therefore MRL SR/EPMAR can be submitted as
537 part of a bibliographic application in accordance with the amending Directive 2004/28/EC even though
538 the Marketing Authorisation may be for non-food producing species.

539 **8.1.3. Pharmacological data**

540 Pharmacological studies in laboratory animals can be replaced by cross reference to the target species
541 studies submitted in Part 4 of the dossier, by means of a summary of any observed effects in the
542 pharmacodynamic studies and a summary of the pharmacokinetics profile to include absorption,
543 distribution, metabolism and excretion (ADME). Absence of studies in laboratory animals must be
544 scientifically justified.

545 **8.1.4. Toxicological data**

546 Toxicological data are required for the assessment of user safety and of adverse effects in the target
547 animals (e.g., possible adverse effects to fertility or reproduction). It should consider potential
548 problems associated with administration, such as exposure by inhalation, dermal contact and
549 accidental self-injection, as necessary. The omission of studies should be adequately justified.

550 Where appropriate, CVMP/VICH guidelines should be followed and the toxicological tests themselves
551 should be conducted in accordance with the relevant OECD guidelines or other internationally
552 recognised guidelines; any deviation should be justified.

553 **8.1.5. User safety assessment**

554 A user risk assessment of the potential hazards and exposure scenarios from administration of the
555 product to animals, and risk management proposals must be submitted for all applications. The
556 requirements of the user safety guideline (EMA/CVMP/543/03-Rev.1) should be applied. This
557 guideline allows for consideration of (low) exposure frequencies. This assessment should include a
558 discussion of the effects found in the pharmacological and toxicological data (i.e., hazard identification)
559 and relate this to the type and extent of human exposure to the product, with a view to formulating
560 appropriate user warnings. For topically-applied products, Guideline EMA/CVMP/SWP/721059/2014
561 should also be applied.

562 **8.1.6. Environmental safety**

563 Environmental safety requirements should be addressed by referring to the CVMP/VICH Phase I
564 guidance as given in CVMP/VICH/592/98-FINAL.

565 **9. Summary tables of data requirements**

566 Table 1. Data requirements for safety testing for establishment of MRLs for minor food-producing
567 species (where no toxicological evaluation has taken place)

568 Table 2. Data requirements for safety testing for a marketing authorisation for minor food-producing
569 species (where the ADI has already been established or was not considered necessary)

570 Table 3. Data Requirements for safety testing for a Marketing Authorisation for non-food-producing
571 species

572 Table 4. Current data requirements for residues studies for MRLs and withdrawal periods

573 Table 5. Current data requirements for analytical methods

574 **Table 1.** Data requirements for safety testing for establishment of MRLs for minor food-producing
 575 species (where no toxicological evaluation has taken place)

Regulation (EC) No. 470/2009	Standard data requirements (6)	Minimum dataset for minor food-producing species
A Safety file		
A2. Pharmacology		
2.1 Pharmacodynamics	Details of pharmacodynamic studies in laboratory animals in the absence of human data	Details of pharmacodynamic studies in laboratory animals in the absence of human data may be necessary on a case by case basis, depending on the substance under consideration. A minimum dataset not including pharmacodynamic studies must be justified.
2.2 Pharmacokinetics	Details of pharmacokinetic studies in laboratory animals, and if available, human data. See VICH GL47.	Same criteria apply.
A3. Toxicological studies	See VICH GL33	
3.1 Single dose toxicity	Not required. Studies may be submitted where they exist in the study archive or in published literature. Cross refer to any other acute toxicity studies (e.g. user safety studies)	Same criteria apply.
3.2 Repeat dose toxicity	<ul style="list-style-type: none"> • 90 day study (See VICH GL31) • 2 species, 1 must be non-rodent • Oral administration • Chronic toxicity study³ (See VICH GL37) 	Same criteria apply.
3.3 Tolerance in the target species	Not required. Relevant data may be submitted if available.	Same criteria apply.
3.4 Reproductive toxicity including developmental toxicity		
3.4.1 Study of the effects on reproduction	See VICH GL22. Usually need a study in at least one	Same criteria apply.

³ The VICH GL37 (Studies to evaluate the safety of residues of veterinary drugs in human food: repeat-dose (chronic) toxicity testing) (CVMP/VICH/468/03-FINAL) indicates that most veterinary drugs will need to be tested for the adverse consequences of chronic exposure, as there is a potential for consumers to be exposed repeatedly throughout their lifetime. However, the guideline does not preclude the possibility of alternative approaches that may offer an equivalent assurance of safety, including scientifically based reasons as to why chronic toxicity testing may not need to be provided

Regulation (EC) No. 470/2009	Standard data requirements (6)	Minimum dataset for minor food-producing species
	species (rat). Oral route of administration.	
3.4.2 Study of developmental toxicity	See VICH GL32	Same criteria apply.
3.5 Genotoxicity	See VICH GL23 (R)	Same criteria apply.
3.6 Carcinogenicity	<p>Long-term animal carcinogenicity bioassays will usually be required for substances to which human beings will be exposed when any of the following criteria apply:</p> <ul style="list-style-type: none"> • where structure-activity relationships indicate a close chemical analogy with known carcinogens; • where findings in toxicity studies have identified potentially pre-neoplastic lesions or are indicative of neoplasia; • where mutagenicity testing produced results indicating a possibility of carcinogenic effects; • See VICH GL28. 	Same criteria apply.
A.4 Studies of Other Effects		
4.1 Immunotoxicity	<p>If immunological effects in repeat dose studies are observed, additional studies are required</p> <p>Additional studies in accordance with current state of scientific knowledge</p>	Same criteria apply.
4.2 Neurotoxicity	<p>Signs of neurotoxicity after acute or subchronic administration of new compounds in laboratory or target animals may require more detailed studies.</p> <ul style="list-style-type: none"> • Required if substance belongs to: organophosphates (OPs), pyrethroids, carbamates, avermectins • Oral route (OECD 424 and 426) 	Same criteria apply.

Regulation (EC) No. 470/2009	Standard data requirements (6)	Minimum dataset for minor food-producing species
	OPs: delayed neurotoxicity: single dose (OECD 418); repeated dose (OECD 419)	
<p>4.3 Microbiological studies</p> <p>4.3.1 potential effects on the human gut flora</p> <p>4.3.2 potential effects on the micro-organisms used for industrial food-processing</p>	<ul style="list-style-type: none"> • Required if there are residues of antimicrobial compounds • See VICH GL36 • Assessment of the effect of antimicrobial substances on dairy starter cultures. See EMEA/CVMP/276/1999 	Same criteria apply.
4.4 Observations in Humans	<p>Observed effects in human therapy medicinal products.</p> <p>All relevant epidemiological, pharmacological, toxicological, and clinical data to be provided.</p>	Same criteria apply.

Table 2. Data requirements for safety testing for a Marketing Authorisation for minor food-producing species (where the ADI has already been established or was not considered necessary)

Annex I of Directive 2001/82/EC as amended by 2009/9/EC ⁴	Standard data requirements: For well-established use applications, the MRL SR/EPMAR may be used, if one exists.	Minimum dataset for minor food-producing species ⁵ For well-established use applications, the MRL SR/EPMAR may be used, if one exists.
PART III.A SAFETY DOCUMENTATION		
III.A.2 Pharmacological studies 2.1 Pharmacodynamics 2.2 Pharmacokinetics	Cross-reference to studies in Part 4. Details of pharmacological studies in laboratory animals and relevant observations in target species.	Same criteria apply.
III.A.3 Toxicological studies		
3.1 Single dose toxicity	<ul style="list-style-type: none"> Data relevant to the assessment of possible effects of accidental administration to humans To reduce animal numbers, alternative validated protocols and internationally recognised protocols will be accepted 	Same criteria apply.
3.2 Repeat dose toxicity	<ul style="list-style-type: none"> 90 day study 2 species, 1 must be non-rodent Oral administration Chronic toxicity study⁶ 	Same criteria apply.
3.3 Tolerance in the target species	Cross-reference to studies in Part 4, Chapter I, Section B.	Same criteria apply.
3.4 Reproductive toxicity including teratogenicity		
3.4.1 Study of the effects on reproduction	Reproduction toxicity study in at least 1 species, usually rodent. See VICH GL22.	Same criteria apply.
3.4.2 Embryotoxic/ foetotoxic effects including teratogenicity	At least 1 study conducted in rats, and a 2 nd study in another mammalian species, depending on the results of the 1 st study. See VICH GL32.	Same criteria apply.
3.5 Genotoxicity	Testing strategy in accordance with current	Same criteria apply.

⁴ Commission Directive 2009/9/EC amending Annex I to Directive 2001/82/EC

⁵ The toxicological data package must allow full assessment of user safety issues and concerns (see CVMP guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1))

⁶ The VICH GL37 (repeat-dose chronic toxicity testing) indicates that most veterinary drugs will need to be tested for the adverse consequences of chronic exposure, as there is a potential for consumers to be exposed repeatedly throughout their lifetime. However, the guideline does not preclude the possibility of alternative approaches that may offer an equivalent assurance of safety, including scientifically based reasons as to why chronic toxicity testing may not need to be provided.

Annex I of Directive 2001/82/EC as amended by 2009/9/EC ⁴	Standard data requirements: For well-established use applications, the MRL SR/EPMAR may be used, if one exists.	Minimum dataset for minor food-producing species ⁵ For well-established use applications, the MRL SR/EPMAR may be used, if one exists.
	state of scientific knowledge (VICH GL23 (R)).	
3.6 Carcinogenicity	<p>2-year carcinogenicity study in rats required if:</p> <ul style="list-style-type: none"> i. active(s) have close chemical analogy with known carcinogens (referred to as 'Structural Alerts'), or, ii. positive mutagenicity tests, or, iii. suspect signs during toxicity testing. <p>Studies designed in accordance with current state of scientific knowledge</p> <p>A 2nd study conducted in mice may also be required, in accordance with guidance (VICH GL28).</p>	Same criteria apply.
III.A.4 Studies of Other Effects		
4.1 Special studies	Special studies including specific target organ toxicity (e.g. immunotoxicity, endocrine function tests, liver and renal function tests, effects on enzymes, neurotoxicity, sensitisation, skin and eye irritation, inhalation toxicity, mechanistic studies, relay toxicity studies, etc. as appropriate).	Same criteria apply.
4.2 Observations in humans	Observed effects following human exposure, if available.	Same criteria apply.
4.3 Microbiological studies	<p>Required for antibacterial compounds.</p> <p>Investigate risk to human intestinal flora and risk of resistance development.</p> <p>Investigate if residues can affect processes in industrial foodstuffs processes.</p>	Same criteria apply.
4.4 Studies on metabolites, impurities, other substances and formulation	Appropriate studies to assess the toxicity of metabolites, impurities, other substances and formulation	Same criteria apply.

Annex I of Directive 2001/82/EC as amended by 2009/9/EC ⁴	Standard data requirements: For well-established use applications, the MRL SR/EPMAR may be used, if one exists.	Minimum dataset for minor food-producing species ⁵ For well-established use applications, the MRL SR/EPMAR may be used, if one exists.
III.A.5 User safety	The requirements of the user safety guideline (EMA/CVMP/543/03-Rev.1) should be applied. For topically-applied products, EMA/CVMP/SWP/721059/2014 should also be applied.	Same criteria apply.
III.A.6 Ecotoxicity	Environmental Risk Assessment (ERA) in accordance with the existing VICH/CVMP (Phase I/II) Guidelines required.	Same criteria apply.

Table 3. Data requirements for safety testing for a Marketing Authorisation for non-food-producing species

Annex I of Directive 2001/82/EC as amended by 2009/9/EC	Standard data requirements: For well-established use applications, the MRL SR/EPMAR may be used, if one exists.	Minimum dataset for minor non-food-producing species For well-established use applications, the MRL SR/EPMAR may be used, if one exists.
PART III.A SAFETY DOCUMENTATION		
III.A.2 Pharmacological studies 2.1 Pharmacodynamics 2.2 Pharmacokinetics	Cross-reference to studies in Part 4. Details of pharmacological studies in laboratory animals and relevant observations in target species	Same criteria apply.
III.A.3 Toxicological studies		
3.1 Single dose toxicity	<ul style="list-style-type: none"> Data relevant to the assessment of possible effects of accidental administration to humans To reduce animal numbers, alternative validated protocols and internationally recognised protocols will be accepted 	Same criteria apply.
3.2 Repeat dose toxicity	<p>Study in 1 species and this may be replaced by an equivalent study in the target species.</p> <p>Tests may be modified (with justification) for new combinations of known substances.</p> <p>See VICH GL31.</p>	Same criteria apply.
3.3 Tolerance in the target species	Cross-reference to studies in Part 4, Chapter I, Section B.	Same criteria apply.
3.4 Reproductive toxicity including teratogenicity.		
3.4.1 Study of the effects on reproduction	Not required.	Same criteria apply.
3.4.2 Embryotoxic/ foetotoxic effects including teratogenicity	<p>A study of developmental toxicity in at least one species may be required. The species selected may be the target species.</p> <p>However, the standard package (see Table 2.) is required if use of the product would result in significant exposure to users.</p> <p>See VICH GL32.</p>	Same criteria apply.
3.5 Genotoxicity	Testing strategy in accordance with current	Same criteria apply.

Annex I of Directive 2001/82/EC as amended by 2009/9/EC	Standard data requirements: For well-established use applications, the MRL SR/EPMAR may be used, if one exists.	Minimum dataset for minor non-food-producing species For well-established use applications, the MRL SR/EPMAR may be used, if one exists.
	state of scientific knowledge (VICH GL23R).	
3.6 Carcinogenicity	<p>Long term carcinogenicity study required if:</p> <ul style="list-style-type: none"> i. active has a close chemical analogy with known carcinogens (referred to as 'Structural Alerts'), or, ii. positive mutagenicity tests, or, iii. suspect signs during toxicity testing. <p>Studies designed in accordance with current state of scientific knowledge.</p> <p>See VICH GL28.</p>	Same criteria apply.
III.A.4 Studies of Other Effects		
4.1 Special studies	Special studies including specific target organ toxicity (e.g. immunotoxicity, endocrine function tests, liver and renal function tests, effects on enzymes, neurotoxicity, sensitisation, skin and eye irritation, inhalation toxicity, mechanistic studies, relay toxicity studies, etc. as appropriate).	Data not required unless relevant effects in repeat dose studies have been observed.
4.2 Observations in humans	Observed effects in human therapy medicinal products.	Same criteria apply.
4.3 Microbiological studies	Not required.	
4.4 Studies on metabolites, impurities, other substances and formulation	Appropriate studies to assess the toxicity of metabolites, impurities, other substances and formulation.	Same criteria apply.
III.A.5 User safety	<p>The requirements of the user safety guideline (EMA/CVMP/543/03-Rev.1) should be applied.</p> <p>For topically-applied products, EMA/CVMP/SWP/721059/2014 should also be applied.</p>	Same criteria apply.

Annex I of Directive 2001/82/EC as amended by 2009/9/EC	Standard data requirements: For well-established use applications, the MRL SR/EPMAR may be used, if one exists.	Minimum dataset for minor non-food-producing species For well-established use applications, the MRL SR/EPMAR may be used, if one exists.
III.A.6 Ecotoxicity	Environmental Risk Assessment (ERA) in accordance with the existing VICH/CVMP (Phase I/II) Guidelines required.	Same criteria apply.

Table 4. Current data requirements for residues studies for MRL and withdrawal periods (see text of document for possibilities for extrapolation)

	Establishment of MRLs (6)		Establishment of withdrawal periods	
	Major Species	Minor Species	Major Species	Minor Species
Meat: Muscle (including injection site), fat (skin+fat for pigs and poultry), liver, kidney. Muscle and skin in natural proportions for fish	<p>Large animals (mammals): 4 animals/time point</p> <p>Poultry: 6 animals/time point</p> <p>Fish: 10 animals/time point</p> <p>(for all species usually 4-5 time points recommended)</p> <p>See VICH GL46</p> <p>Extrapolation is also possible. See criteria in Regulation 2017/880⁷</p>	<p>A residues depletion study with 1-4 animals and a sampling timepoint where tissue concentrations are predicted to be close to the MRL</p> <p>Extrapolation is also possible. See criteria in Regulation 2017/880⁷</p>	<p>Minimum 4 animals/time point at a minimum of 4 time points as stated in VICH GL48 (R)</p>	<p>No specific conditions for minor species.</p> <p>Under certain conditions, withdrawal periods could be extrapolated from major species. See main text.</p>
Milk	<p>≥8 as in VICH GL4</p> <p>Extrapolation is also possible. See criteria in Regulation 2017/880⁷</p>	<p>No specific conditions for minor milk-producing species.</p> <p>Extrapolation is also possible. See criteria in Regulation 2017/880⁷</p>	<p>Samples of milk from at least 20 animals, as set out in VICH GL48 (R)</p>	<p>No specific conditions for minor milk-producing species.</p> <p>Under certain conditions, withdrawal periods could be extrapolated from major species. See main text.</p>
Egg	<p>≥10 eggs/day for laying birds over a sufficiently long time period.</p> <p>VICH GL46</p>	<p>No specific conditions for minor eggs-producing species.</p> <p>Extrapolation is also possible. See criteria in Regulation 2017/880⁷</p>	<p>At least 10 eggs per time point, as set out in VICH GL48 (R)</p>	<p>No specific conditions for minor egg-producing species.</p> <p>Under certain conditions, withdrawal periods could be extrapolated from</p>

⁷ It should be noted the possible extrapolation of MRLs recommended in one species/food commodity to a second species/food commodity is considered by CVMP as part of its evaluation of the application for the establishment of MRLs in the first species. While applicants can provide data to support the extrapolation of proposed MRLs, companies cannot make stand-alone applications for the extrapolation of established MRLs.

Establishment of MRLs (6)			Establishment of withdrawal periods	
				major species. See main text.
Honey	6 colonies per site, 4 sites. See VICH GL56		6 colonies per site, 4 sites. See VICH GL56	

582 **Table 5.** Current data requirements for analytical methods

Routine Analytical Method proposed for residues monitoring		Analytical Method validation for withdrawal period	
Major Species	Minor Species	Major Species	Minor Species
<p>LOD (n > 20 blank samples)</p> <p>LOQ (as per VICH GL49)</p> <p>Accuracy: 3 analyte levels (1/2MRL-2xMRL), n=6/level</p> <p>Precision:</p> <p>Repeatability: 3 analyte levels (1/2MRL, MRL, 2xMRL), n=6/level</p> <p>Within Laboratory Reproducibility 3 analyte levels (1/2MRL, MRL, 2xMRL), n=6 at n ≥ 3 separate days</p> <p>Specificity against homologues/analogues</p>	<p>Determination of LOQ, accuracy and precision can be combined</p> <p>The method should be validated in respect of the LOQ and for accuracy and precision at the level of the MRL and half the MRL.</p> <p>With regard to specificity, possible interference from matrix components and from chemically closely related substances used in veterinary medicine should be investigated.</p> <p>Adequate storage and sample processing stability data should also be supplied.</p>	<p>See VICH GL49.</p>	<p>See VICH GL49.</p>

583 References

584 The following legislation, guidelines and notes for guidance are relevant to this guideline:

- 585 1. Revised Policy on Classification and Incentives for Veterinary Medicinal Products indicated for Minor
586 use Minor species (MUMS)/limited market
587 (EMA/308411/2014) [http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_p
588 rocedural_guideline/2014/09/WC500172928.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/09/WC500172928.pdf)
- 589 2. Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the
590 Community code relating to veterinary medicinal
591 products [http://ec.europa.eu/health/files/eudralex/vol-
592 5/dir_2001_82/dir_2001_82_cons2009_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-5/dir_2001_82/dir_2001_82_cons2009_en.pdf)
- 593 3. Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying
594 down Community procedures for the establishment of residue limits of pharmacologically active
595 substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and
596 amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC)
597 726/2004 of the European Parliament and of the
598 Council http://ec.europa.eu/health/files/eudralex/vol-5/reg_2009-470/reg_470_2009_en.pdf
- 599 4. Directive 2010/63/EC (regarding the protection of animals used for experimental and other
600 scientific purposes).
- 601 5. Commission Regulation (EU) 2017/880 of 23 May 2017 laying down rules on the use of a
602 maximum residue limit established for a pharmacologically active substance in a particular
603 foodstuff for another foodstuff derived from the same species and a maximum residue limit
604 established for a pharmacologically active substance in one or more species for other species, in
605 accordance with Regulation (EC) No 470/2009 of the European Parliament and of the Council
- 606 6. Commission Regulation 2018/782 establishing the methodological principles for the risk
607 assessment and risk management recommendations referred to in Regulation (EC) No 470/2009
- 608 7. CVMP and VICH safety and residues guidelines, available
609 at: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_00
610 0192.jsp&mid=WC0b01ac058002dd31](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000192.jsp&mid=WC0b01ac058002dd31):
- 611 • CVMP Guideline on environmental impact assessment for veterinary medicinal products in
612 support of the VICH guidelines GL6 and GL38 (EMA/CVMP/ERA/418282/2005-Rev.1-Corr)
 - 613 • CVMP Guideline on user safety for pharmaceutical veterinary medicinal products
614 (EMA/CVMP/543/03-Rev.1)
 - 615 • CVMP Guideline on user safety of topical administered products
616 (EMA/CVMP/SWP/721059/2014)
 - 617 • CVMP Note for guidance for the assessment of the effect of antimicrobial substances on dairy
618 starter cultures (EMA/CVMP/276/99-FINAL)
 - 619 • CVMP Note for guidance on the establishment of maximum residue limits for minor animal
620 species (EMA/CVMP/153a/97-FINAL)
 - 621 • CVMP Note for guidance on the establishment of maximum residue limits for Salmonidae and
622 other fin fish (EMA/CVMP/153b/97-FINAL)

- 623 • CVMP Note for guidance on the risk analysis approach for residues of veterinary medicinal
624 products in food of animal origin (EMA/CVMP/187/00-FINAL).
- 625 • VICH GL6: Environmental Impact Assessment (EIAs) for Veterinary Medicinal Products –
626 Phase I (CVMP/VICH/592/98-FINAL)
- 627 • VICH GL22: Studies to evaluate the safety of residues of veterinary drugs in food: reproduction
628 testing (CVMP/VICH/525/2000)
- 629 • VICH GL23: Studies to evaluate the safety of residues of veterinary drugs in food: genotoxicity
630 testing (CVMP/VICH/526/2000)
- 631 • VICH GL28: Studies to evaluate the safety of residues of veterinary drugs in food:
632 carcinogenicity testing (CVMP/VICH/645/2001 Rev.1)
- 633 • VICH GL31: Studies to evaluate the safety of residues of veterinary drugs in food: repeat-dose
634 (90 days) toxicity testing (CVMP/VICH/484/2002)
- 635 • VICH GL32: Studies to evaluate the safety of residues of veterinary drugs in food:
636 developmental toxicity testing (CVMP/VICH/485/2002)
- 637 • VICH GL33: Studies to evaluate the safety of residues of veterinary drugs in human food:
638 general approach to testing (EMA/CVMP/VICH/486/02-Rev.2)
- 639 • VICH GL36: Studies to evaluate the safety of residues of veterinary drugs in food: General
640 approach to establish a microbiological ADI (EMA/CVMP/VICH/467/2003)
- 641 • VICH GL37: Studies to evaluate the safety of residues of veterinary drugs in human food:
642 repeat-dose (chronic) toxicity testing (CVMP/VICH/468/03-FINAL)
- 643 • VICH GL38: Environmental Impact Assessment for Veterinary Medicinal Products –
644 Phase II (CVMP/VICH/790/03-FINAL)
- 645 • VICH GL46: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in
646 food-producing animals: metabolism study to determine the quantity and identify the nature of
647 residues (EMA/CVMP/VICH/463072/2009)
- 648 • VICH GL47: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in
649 food-producing animals: laboratory animal comparative metabolism studies
650 EMA/CVMP/VICH/463104/2009)
- 651 • VICH GL48 (R): Studies to evaluate the metabolism and residue kinetics of veterinary drugs in
652 food-producing animals: marker residue depletion studies to establish product withdrawal
653 periods
- 654 • VICH GL49: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in
655 food-producing animals: validation of analytical methods used in residue depletion studies
656 (EMA/CVMP/VICH/463202/2009)
- 657 • VICH GL56: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in
658 food-producing animals: study design recommendations for residue studies in honey for
659 establishing MRLs and withdrawal periods (EMA/CVMP/VICH/176637/2014)
- 660 • VICH GL57: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in
661 food-producing species: marker residue depletion studies to establish product withdrawal
662 periods in aquatic species (Draft: EMA/CVMP/VICH/517152/2013)

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