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3 Committee for Veterinary Medicinal Products (CVMP)

4 **Guideline on stability testing for applications for variations**
5 **to a marketing authorisation for veterinary medicinal**
6 **products**
7 **Draft**

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9 This guideline replaces the Guideline on stability testing for applications for variations to a marketing
10 authorisation (EMA/CHMP/CVMP/QWP/441071/2011- Rev.2) for veterinary medicinal products. For
11 human medicinal products EMA/CHMP/CVMP/QWP/441071/2011- Rev.2 still applies.

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13 Comments should be provided using this EUSurvey [form](#). For any technical issues, please contact
the [EUSurvey Support](#).

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Keywords	<i>Stability, stability testing, stability data, veterinary medicinal products, variations, Regulation (EU) 2019/6</i>
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16 **to a marketing authorisation for veterinary medicinal**
17 **products**

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121 **Executive summary**

122 This guideline provides guidance on the stability data which have to be generated in order to support a
123 variation to a marketing authorisation for veterinary medicinal products. The guideline provides
124 general guidance on stability testing for variations not requiring assessment (VNRA) and variations
125 requiring assessment (VRA).

126 **1. Introduction (background)**

127 This guideline describes the stability testing requirements for variations to a marketing authorisation
128 for veterinary medicinal products after approval. This guideline is an extension of the CVMP Guidelines
129 on stability testing of existing active substances and related finished products and the respective VICH
130 Guidelines for new active substances and drug products.

131 The guideline seeks to illustrate the stability data required for variations to active substances and/or
132 finished products. It is not always necessary to comply with this guideline when there are scientifically
133 justifiable reasons for using alternative approaches (e.g., quality by design concept). However, the
134 stability data outlined in this guideline reflects the usual expectation of the regulators.

135 While the guideline provides a general indication on the requirements for stability testing, it allows
136 sufficient flexibility to encompass the variety of different practical situations required for specific
137 scientific situations and characteristics of the material being evaluated.

138 **2. Scope**

139 The purpose of this guideline is to outline the stability data which have to be generated in case of
140 variations. It is applicable to chemical active substances and related finished products, herbal
141 substances, herbal preparations and related herbal medicinal products for veterinary use. Biologicals,
142 immunologicals and products derived from biotechnology are not within the scope of this guideline.

143 Variations for active substances and finished products encompass a wide range of situations. The
144 Guideline provides general guidance on stability testing in case of variations requiring and not requiring
145 assessment.

146 **3. Legal basis**

147 This guideline should be utilised in conjunction with the Veterinary Medicinal Products Regulation
148 (Regulation (EU) 2019/6), the Commission Implementing Regulation (EU) 2021/17 establishing a list
149 of variations not requiring assessment and the Guidance on the details of the classification of variations
150 requiring assessment (EMA/CMDv/7381/2021).

151 **4. General requirements**

152 In cases of variations which require generation of stability data on the finished product or the active
153 substance, the stability studies required, including commitment batches, should always be continued
154 up to the approved shelf-life / retest period and the authorities should be informed immediately if any
155 problems with the stability appear during storage, e.g. if outside specification or potentially outside
156 specification.

157 The scope and design of the stability studies for variations and changes are based on the knowledge
158 and experience acquired of the active substances and finished products. The available information
159 must be taken into account such as:

160 a. For active substances:

- 161 • the stability profile including the results of stress testing, if applicable (except herbals);
- 162 • the supportive data;
- 163 • the primary data of long term and accelerated* testing.

164 b. For finished products:

- 165 • the supportive data;
- 166 • the primary data of long term and accelerated* testing.

167 In all variations, the applicant assesses whether the intended change has the potential to impact the
168 quality characteristics and stability of the active substances and/or the finished products and
169 consequently on their stability.

170 When stability data are required, the choice of test conditions, defined in this guideline refers to

- 171 • the CVMP/VICH Guideline on Stability Testing of New Veterinary Drug Substances and
172 Medicinal Products (VICH GL3)
- 173 • and the CVMP/QWP Guideline on Stability Testing of Existing Active Substances and Related
174 Finished Products (EMA/CVMP/QWP/709423/2022), respectively.

175 Where appropriate, the concept of bracketing and matrixing as described in the CVMP/VICH Guideline
176 on Bracketing and Matrixing Designs for Stability Testing of Veterinary Drug Substances and Medicinal
177 Products (VICH GL45) may be applied across related products.

178 The results of stability studies of the varied active substance/finished product, including the requested
179 time period as defined below, using long term and accelerated* testing conditions, should be compared
180 to studies performed on the unchanged active substance/finished product. This ensures that the
181 change does not negatively impact the stability profile, i.e. that the specification limits of the active
182 substance/finished product will still be met at the end of the proposed retest period/shelf-life. The
183 comparison data of the unchanged product submitted with the variation may come from previous
184 studies.

185 In relation to herbal substances, herbal preparations and related herbal medicinal products the
186 guideline on quality of herbal medicinal products / traditional herbal medicinal products
187 (EMA/HMPC/CHMP/CVMP/201116/2005), the guideline on specifications: test procedures and
188 acceptance criteria for herbal substances, herbal preparations and herbal medicinal products /
189 traditional herbal medicinal products (EMA/HMPC/CHMP/CVMP/162241/2005) should also apply. The
190 testing of herbal substances and herbal preparations, testing at accelerated storage conditions or at
191 the intermediate storage conditions may be omitted if justified by the applicant and if the storage
192 conditions below 25° C are clearly labelled on the product.

193 Where extrapolation of data is applicable, see Annex II for further information.

194 **5. Variations not requiring assessment**

195 If a variation to a marketing authorisation fulfils the conditions defined in the Commission
196 Implementing Regulation (EU) 2021/17 establishing a list of variations not requiring assessment and if

197 stability data are required, the minimum set of data to be submitted with the variation is defined within
198 this Commission Implementing Regulation.

199 **6. Variations requiring assessment**

200 Variations requiring assessment are listed in the Guidance on the details of the classification of
201 variations requiring assessment (EMA/CMDv/7381/2021). These variations have different levels of
202 complexity and thus supporting data for particular variations will depend on the exact nature of the
203 change.

204 For certain variations requiring assessment, typically with reduced timetable (VRA-R), recommended
205 documentation is listed in the guidance. Where a change may impact stability, the required stability
206 data at the time of submission are specified. For the VRA-R "z"-variations, which scopes are not
207 specifically described in the classification guidance, the required stability data has to be decided on a
208 case by case basis. However, consideration should be given to specified requirements for any other
209 similar changes which have actually been included in the guidance.

210 For the other variations requiring assessment, typically with standard or extended timetable (VRA-S
211 and VRA-E), data to be submitted with these variations are not defined in the guidance in the majority
212 of cases. The stability data outlined below should be part of the documentation at submission of these
213 variations.

214 **6.1. (F.I.a.1.a) Change in the manufacturer of a** 215 **starting material/reagent/intermediate used in the manufacturing process** 216 **of the active substance or change in the manufacturer (including where** 217 **relevant quality control testing sites) of the active substance, where no Ph.** 218 **Eur. certificate of suitability is part of the approved dossier: Introduction of** 219 **a manufacturer of active substance supported by an ASMF**

220 In case of an introduction of a manufacturer of the active substance that is supported by an ASMF
221 stability data should be included in the applicant's part of the ASMF.

222 In relation to stability data of the active substance, the recommendations given in the Guideline on
223 stability testing of existing active substances and related finished products
224 (EMA/CVMP/QWP/709423/2022) should be utilised.

225 If the quality characteristics (e.g. physical characteristics, impurity profile) of the active substance are
226 changed in a way that may impact the stability of the finished product, additional six months stability
227 data from at least two batches of finished product, of at least pilot scale, under long term and
228 accelerated* conditions, are recommended.

229 **6.2. (F.I.a.1.b) Change in the manufacturer of a** 230 **starting material/reagent/intermediate used in the manufacturing process** 231 **of the active substance or change in the manufacturer (including where** 232 **relevant quality control testing sites) of the active substance, where no Ph.** 233 **Eur. certificate of suitability is part of the approved dossier: The proposed** 234 **manufacturer uses a substantially different route of synthesis or** 235 **manufacturing conditions, which may have a potential to change important** 236 **quality characteristics of the active substance, such as qualitative and/or**

237 **quantitative impurity profile requiring qualification, or physico-chemical**
238 **properties impacting on bioavailability**

239 In relation to stability data of the active substance, the recommendations given in the Guideline on
240 stability testing of existing active substances and related finished products
241 (EMA/CVMP/QWP/709423/2022) should be utilised.

242 If the quality characteristics (e.g. physical characteristics, impurity profile) of the active substance are
243 changed in a way that may impact the stability of the finished product, additional six months stability
244 data from at least two batches of finished product, of at least pilot scale, under long term and
245 accelerated* testing conditions, are recommended.

246 **6.3. (F.I.a.1.e) Change in the manufacturer of a**
247 **starting material/reagent/intermediate used in the manufacturing process**
248 **of the active substance or change in the manufacturer (including where**
249 **relevant quality control testing sites) of the active substance, where no Ph.**
250 **Eur. certificate of suitability is part of the approved dossier: Introduction of**
251 **a new manufacturer of the active substance that is not supported by an**
252 **ASMF and requires significant update to the relevant active substance**
253 **section of the dossier**

254 In relation to stability data of the active substance, the recommendations given in the Guideline on
255 stability testing of existing active substances and related finished products
256 (EMA/CVMP/QWP/709423/2022) should be utilised. If the quality characteristics (e.g. physical
257 characteristics, impurity profile) of the active substance are changed in a way that may impact the
258 stability of the finished product, additional six months of stability data from at least two batches of
259 finished product, of at least pilot scale, under long term and accelerated* testing conditions, are
260 recommended.

261 **6.4. (F.I.a.2.a) Changes in the manufacturing process of the active**
262 **substance: Substantial changes to the manufacturing process of the active**
263 **substance which may have a significant impact on the quality, safety or**
264 **efficacy of the medicinal product**

265 In variations to the manufacturing process of the active substance, the following approaches may be
266 considered as acceptable:

267 If the quality characteristics (e.g. physical characteristics, impurity profile) of the active substance are
268 changed in a way that stability may be compromised, comparative stability data are recommended in
269 long term and accelerated* testing conditions, on the active substance before and after the change:

- 270
- for active substances known to be stable: three months data on at least one batch of at least
271 pilot scale batch size (see Annex I for the definition of stable active substance).
 - for active substances known to be unstable: six months data on at least three batches of at
272 least pilot scale batch size.
273

274 If the quality characteristics (e.g. physical characteristics, impurity profile) of the active substance are
275 changed in a way that may impact the stability of the finished product, additional six months of
276 stability data from at least two batches of finished product, of at least pilot scale, under long term and
277 accelerated* testing conditions, are recommended.

278 **6.5. (F.I.a.2.c) Changes in the manufacturing process of the active**
279 **substance: The change relates to a herbal medicinal product and there is a**
280 **change to any of the following: geographical source, manufacturing route**
281 **or production**

282 In variations to the manufacturing process of the active substance, the following approaches may be
283 considered as acceptable:

284 If the quality characteristics (e.g. physical characteristics, impurity profile) of the active substance are
285 changed in a way that stability may be compromised, comparative stability data are recommended in
286 long term and accelerated* term testing conditions, on the active substance before and after the
287 change:

- 288 • for active substances known to be stable: three months data on at least one batch of at least
289 pilot scale batch size (see Annex I for the definition of stable active substance).
- 290 • for active substances known to be unstable: six months data on at least three batches of at
291 least pilot scale batch size.

292 If the quality characteristics of the active substance are changed in a way that may impact the stability
293 of the finished product, additional six months of stability data from at least two batches of finished
294 product, of at least pilot scale, under long term and accelerated* testing conditions, are recommended.

295 **6.6. (F.I.c.1.a) Change in immediate packaging of the active substance:**
296 **Qualitative and/or quantitative composition for sterile and non-frozen**
297 **biological/immunological active substances**

298 (Note: According to the scope this guideline is not applicable to biological/immunological active
299 substances). In case of a change to the immediate packaging of a sterile active substance the following
300 approach may be considered as acceptable: Comparative stability data are required using long term
301 and accelerated* testing conditions of six months in duration on at least 2 batches of at least pilot
302 scale of the active substance.

303 **6.7. (F.I.f.1) Substantial changes in the updated version of the ASMF or the**
304 **active substance part of the dossier**

305 Depending on the scope of the changes and when the stability of the active substance is concerned,
306 stability data should be provided following the same principles described for the relevant changes
307 under code F.I.

308 **6.8. (F.II.a.3.b.1) Change in composition (excipients) of the finished**
309 **product: Qualitative or quantitative changes in one or more excipients that**
310 **may have a significant impact on the safety, quality or efficacy of the**
311 **medicinal product.**

312 In case of a change in the composition of the finished product, the following approaches may be
313 considered as acceptable: For conventional dosage forms (e.g. conventional release solid dosage form,
314 solutions) and when the active substance is known to be stable, comparative stability data, 6 months
315 in duration, under long term and accelerated* testing conditions, on at least two batches of at least
316 pilot scale, are recommended. For critical dosage forms (e.g. modified release form) or when the active
317 substance is known to be unstable, comparative stability data, 6 months in duration, under long term
318 and accelerated* stability testing conditions, on at least three primary batches are recommended. Two
319 of the three batches should be at least pilot scale; the third batch may be smaller.

320 **6.9. (F.II.a.4.a) Change in coating weight of oral dosage forms or change in**
321 **weight of capsule shells: Gastro-resistant, modified or prolonged release**
322 **pharmaceutical forms where the coating is a critical factor for the release**
323 **mechanism**

324 In variations to the coating weight of oral dosage forms, the following approach may be considered as
325 acceptable: Comparative stability data, 6 months in duration, long term and accelerated* stability
326 testing conditions on at least three primary batches are recommended. Two of the three batches
327 should be at least pilot scale; the third batch may be smaller.

328 **6.10. (F.II.a.5.) Change in concentration of a single-dose, total use**
329 **parenteral product, where the amount of the active substance per unit dose**
330 **(i.e. the strength) remains the same**

331 In variations in concentration of single-dose, total use parenteral product, the following approaches
332 may be considered as acceptable:

333 Comparative stability data, 6 months in duration, long term and accelerated* stability testing
334 conditions on at least three primary batches are recommended. Two of the three batches should be at
335 least pilot scale; the third batch may be smaller.

336 **6.11. (F.II.b.1.a) Replacement or addition of a manufacturing site for part**
337 **or all of the manufacturing process of the finished product: Site where any**
338 **manufacturing operation(s) take place, except batch release, batch control,**
339 **and secondary packaging, for biological/immunological medicinal products,**
340 **or for pharmaceutical forms manufactured by complex manufacturing**
341 **processes**

342 (Note: According to the scope this guideline is not applicable to biological/immunological active
343 substances and related finished products).

344 In variations (replacement or addition) to a manufacturing site for part or all of the manufacturing
345 process of the finished product, the following approaches may be considered as acceptable:

346 If the quality characteristics (e.g. physical characteristics, impurity profile) of the finished product are
347 changed in a way that stability may be compromised, comparative stability data are recommended in
348 long term and accelerated* testing conditions, on the finished product before and after the change:

349 For conventional dosage forms (e.g. conventional release solid dosage form, solutions) and when the
350 active substance is known to be stable, comparative stability data, 6 months in duration, under long
351 term and accelerated* testing conditions, on at least two batches of at least pilot scale, are
352 recommended.

353 For critical dosage forms (e.g. modified release form) or when the active substance is known to be
354 unstable, comparative stability data, 6 months in duration, under long term and accelerated* stability
355 testing conditions, on at least three primary batches, are recommended. Two of the three batches
356 should be at least pilot scale; the third batch may be smaller.

357 **6.12. (F.II.b.3.b) Change in the manufacturing process of the finished**
358 **product, including an intermediate used in the manufacture of the finished**
359 **product: Substantial changes to a manufacturing process that may have a**

360 ***significant impact on the quality, safety and efficacy of the medicinal***
361 ***product***

362 In variations to the manufacturing process of the finished product, the following approaches may be
363 considered as acceptable:

364 If the quality characteristics (e.g. physical characteristics, impurity profile) of the finished product are
365 changed in a way that stability may be compromised, comparative stability data are recommended in
366 long term and accelerated* testing conditions, on the finished product before and after the change:

367 For conventional dosage forms (e.g. conventional release solid dosage form, solutions) and when the
368 active substance is known to be stable, comparative stability data, 6 months in duration, under long
369 term and accelerated* testing conditions, on at least two batches of at least pilot scale, are
370 recommended.

371 For critical dosage forms (e.g. modified release form) or when the active substance is known to be
372 unstable, comparative stability data, 6 months in duration, under long term and accelerated* stability
373 testing conditions, on at least three primary batches, are recommended. Two of the three batches
374 should be at least pilot scale; the third batch may be smaller.

375 ***6.13. (F.II.b.3.d) - Change in the manufacturing process of the finished***
376 ***product, including an intermediate used in the manufacture of the finished***
377 ***product: Introduction of a non-standard terminal sterilisation method***

378 In variations to the manufacturing process of the finished product, the following approaches may be
379 considered as acceptable:

380 If the quality characteristics (e.g., impurity profile) of the finished product are changed in a way that
381 stability may be compromised, comparative stability data are recommended in long term and
382 accelerated* testing conditions, on the finished product before and after the change:

383 For conventional dosage forms (e.g. solutions) and when the active substance is known to be stable,
384 comparative stability data, 6 months in duration, under long term and accelerated* testing conditions,
385 on at least two batches of at least pilot scale, are recommended.

386 For critical dosage forms (e.g. suspensions or emulsions for injection) or when the active substance is
387 known to be unstable, comparative stability data, 6 months in duration, under long term and
388 accelerated* stability testing conditions, on at least three primary batches, are recommended. Two of
389 the three batches should be at least pilot scale; the third batch may be smaller.

390 ***6.14. (F.II.b.3.e) Change in the manufacturing process of the finished***
391 ***product, including an intermediate used in the manufacture of the finished***
392 ***product: introduction or increase in the overage that is used for the active***
393 ***substance***

394 In variations to the manufacturing process of the finished product, the following approaches may be
395 considered as acceptable: If the quality characteristics (e.g. content of active substance) of the
396 finished product are changed in a way that stability may be compromised, comparative stability data
397 are recommended in long term and accelerated* testing conditions, on the finished product before and
398 after the change: For conventional dosage forms (e.g. conventional release solid dosage form,
399 solutions) and when the active substance is known to be stable, comparative stability data, 6 months
400 in duration, under long term and accelerated* testing conditions, on at least two batches of at least
401 pilot scale, are recommended. For critical dosage forms (e.g. modified release form) or when the active

402 substance is known to be unstable, comparative stability data, 6 months in duration, under long term
403 and accelerated* stability testing conditions, on at least three primary batches, are recommended. Two
404 of the three batches should be at least pilot scale; the third batch may be smaller.

405 **6.15. (F.II.b.3.h) Change in the manufacturing process of the finished**
406 **product, including an intermediate used in the manufacture of the finished**
407 **product: Change in the holding time of an intermediate or bulk product (if**
408 **applicable)**

409 In variations to the holding time of an intermediate or bulk product, the change should be supported
410 by appropriate stability data following the requirements of the Guideline on manufacture of the
411 veterinary finished dosage form (EMA/CVMP/QWP/798401/2015), section 4.3.

412 **6.16. (F.II.b.4.b) Change in the batch size (including batch size ranges) of**
413 **the finished product: The change relates to all other pharmaceutical forms**
414 **manufactured by complex manufacturing processes**

415 In variations to the batch size of the finished product, the following approaches may be considered as
416 acceptable:

417 If the quality characteristics (e.g. impurity profile) of the finished product are changed in a way that
418 stability may be compromised, comparative stability data are recommended in long term and
419 accelerated* testing conditions, on the finished product before and after the change:

420 For conventional dosage forms manufactured by a complex manufacturing process and when the active
421 substance is known to be stable, comparative stability data, 6 months in duration, under long term and
422 accelerated* testing conditions, on at least two batches of at least pilot scale, are recommended.

423 For critical dosage forms (e.g. modified release form) or when the active substance is known to be
424 unstable, comparative stability data, 6 months in duration, under long term and accelerated* stability
425 testing conditions, on at least three primary batches, are recommended. Two of the three batches
426 should be at least pilot scale; the third batch may be smaller.

427 **6.17. (F.II.e.1.a.2) Change in immediate packaging of the finished product:**
428 **Qualitative and quantitative composition: Sterile medicinal products and**
429 **biological/immunological medicinal products**

430 (Note: According to the scope this guideline is not applicable to biological/immunological active
431 substances and related finished products).

432 In case of a change to the immediate packaging of the finished product the following approach may be
433 considered as acceptable:

434 In the case of less protective packaging or when a risk of interaction occurs for a sterile medicinal
435 product, comparative stability data are recommended using long term and accelerated* testing
436 conditions, of six months in duration, on at least three primary batches of the finished product. Two of
437 the three batches should be at least pilot scale; the third batch may be smaller.

438 **6.18. (F.II.e.1.a.3) Change in immediate packaging of the finished product:**
439 **Qualitative and quantitative composition: The change relates to a less**

440 **protective pack where there are associated changes in storage conditions**
441 **and/or reduction in shelf life.**

442 In case of a change to the immediate packaging of the finished product the following approach may be
443 considered as acceptable:

444 In the case of less protective packaging or when a risk of interaction occurs, mainly for semi-solid or
445 liquid dosage forms, comparative stability data are recommended using long term and accelerated*
446 testing conditions, of six months in duration, on at least three primary batches of the finished product.
447 Two of the three batches should be at least pilot scale; the third batch may be smaller.

448 **6.19. (F.II.e.1.b.2) Change in immediate packaging of the finished product:**
449 **Change in type of container or addition of a new container: Sterile**
450 **medicinal products and biological/immunological medicinal products**

451 (Note: According to the scope this guideline is not applicable to biological/immunological active
452 substances and related finished products).

453 In case of a change to the immediate packaging of the finished product the following approach may be
454 considered as acceptable:

455 In the case of less protective packaging or when a risk of interaction occurs, mainly for semi-solid or
456 liquid dosage forms, comparative stability data are recommended using long term and accelerated*
457 testing conditions, of six months in duration, on at least three primary batches of the finished product.
458 Two of the three batches should be at least pilot scale; the third batch may be smaller.

459 **6.20. (F.II.e.4.a) Change in shape or dimensions of the container or closure**
460 **(immediate packaging): The change in shape or dimensions concerns a**
461 **fundamental part of the packaging material, which may have a significant**
462 **impact on the delivery, use, safety or stability of the finished product**

463 In variations to the immediate packaging of the finished product, which may have a significant impact
464 of the stability of the finished product, the following approach may be considered as acceptable:

465 If the quality characteristics (e.g. impurity profile) of the finished product are changed in a way that
466 stability may be compromised, comparative stability data are recommended in long term and
467 accelerated* testing conditions, on the finished product before and after the change:

468 For conventional dosage forms manufactured by a complex manufacturing process and when the active
469 substance is known to be stable, comparative stability data, 6 months in duration, under long term and
470 accelerated* testing conditions, on at least two batches of at least pilot scale, are recommended.

471 For critical dosage forms (e.g. modified release form) or when the active substance is known to be
472 unstable, comparative stability data, 6 months in duration, under long term and accelerated* stability
473 testing conditions, on at least three primary batches, are recommended. Two of the three batches
474 should be at least pilot scale; the third batch may be smaller.

475 **6.21. (F.II.e.5.b) Change in pack size of the finished product: Change in fill**
476 **weight/fill volume of sterile multidose (or single-dose) parenteral**
477 **medicinal product, including biological/immunological medicinal products**

478 (Note: According to the scope this guideline is not applicable to biological/immunological active
479 substances and related finished products).

480 In case of such a change to the pack size of the finished product the following approach may be
481 considered as acceptable:

482 If the quality characteristics (e.g. impurity profile) of the finished product are changed in a way that
483 stability may be compromised, comparative stability data are recommended in long term and
484 accelerated* testing conditions, on the finished product before and after the change:

485 Comparative stability data are recommended using long term and accelerated* testing conditions of six
486 months in duration on at least three primary batches of the finished product. Two of the three batches
487 should be at least pilot scale; the third batch may be smaller.

488 **6.22. (I.I.1.a) Changes to the active substance(s): Replacement of a**
489 **chemical active substance by a different salt/ester/complex/derivative,**
490 **with the same therapeutic moiety, where the efficacy/safety**
491 **characteristics are not significantly different**

492 In case of change to the active substance concerning replacement of a chemical active substance by a
493 different salt, ester, complex or derivative with the same therapeutic moiety, the long-term and
494 accelerated* stability data should be presented for the active substance and for the related finished
495 product in accordance with the Guideline on stability testing of existing active substances and related
496 finished products (EMA/CVMP/QWP/709423/2022).

497 **6.23. (I.I.1.b) Changes to the active substance(s): Replacement by a**
498 **different isomer, a different mixture of isomers, of a mixture by an isolated**
499 **isomer (e.g. racemate by a single enantiomer), where the efficacy/safety**
500 **characteristics are not significantly different**

501 In case of change to the active substance concerning replacement by a different isomer, a different
502 mixture of isomers or of a mixture by an isolated isomer, the long-term and accelerated* stability data
503 should be presented for the active substance and for the related finished product in accordance with
504 the Guideline on stability testing of existing active substances and related finished products
505 (EMA/CVMP/QWP/709423/2022).

506 **6.24. (I.I.1.f) Changes to the active substance(s): Change to the extraction**
507 **solvent or the ratio of herbal drug to herbal drug preparation where the**
508 **efficacy/safety characteristics are not significantly different**

509 In case of change to the active substance concerning changes to the extraction solvent or the ratio of
510 herbal drug to herbal drug preparation, the long-term and accelerated* stability data should be
511 presented for the active substance and for the related finished product in accordance with the
512 Guideline on quality of herbal medicinal products/traditional herbal medicinal products
513 (EMA/HMPC/CHMP/CVMP/201116/2005).

514 **6.25. (I.II.1.c) Changes to strength, pharmaceutical form and route of**
515 **administration: Change or addition of a new strength/potency**

516 In case of change or addition of a new strength/potency for veterinary medicinal products, long-term
517 and accelerated* stability data product should be presented on the finished product in accordance with
518 the Guideline on stability testing of existing active substances and related finished products
519 (EMA/CVMP/QWP/709423/2022).

520 **6.26. (I.II.1.d) Changes to strength, pharmaceutical form and route of**
521 **administration: Change or addition of a new pharmaceutical form**

522 In case of change or addition of a new pharmaceutical form of veterinary medicinal products, long-
523 term and accelerated* stability data should be presented on the finished product in accordance with
524 the Guideline on stability testing of existing active substances and related finished products
525 (EMA/CVMP/QWP/709423/2022).

526 **7. Commitment batches**

527 For variations not requiring assessment and for certain variations requiring assessment, where
528 recommended documentation is listed in the classification guidance (typically VRA-R), that require the
529 generation of stability data on the finished product, adequate follow up studies on commitment batches
530 are necessary.

531 For variations requiring assessment under codes F, where recommended documentation is not listed in
532 the classification guidance (typically VRA-S), that require the generation of stability data on the
533 finished product, at least the first production scale batch manufactured according to the approved
534 variation should be placed on long term stability testing protocol. The stability testing protocol is as
535 described in the original application unless it has previously been varied. Stability studies need to be
536 continued to cover the entire shelf life. The results of these stability studies should be made available
537 on request and the authorities should be informed if any problems appear with the stability studies.

538 For variations requiring assessment under codes I, adequate follow up studies on commitment batches
539 are necessary as described in the Guideline on Stability Testing of Existing Active Substances and
540 Related Finished Products (EMA/CVMP/QWP/709423/2022), section 2.2.8.

541 **References**

- 542 • Commission Implementing Regulation (EU) 2021/17 establishing a list of variations not requiring
543 assessment
- 544 • Guidance on the details of the classification of variations requiring assessment
545 (EMA/CMDv/7381/2021)
- 546 • Guideline on Stability Testing of Existing Active Substances and Related Finished Products
547 (EMA/CVMP/QWP/709423/2022)
- 548 • Guideline on Stability Testing of New Veterinary Drug Substances and Medicinal Products
549 (CVMP/VICH/899/99-VICH GL3)
- 550 • Bracketing and matrixing designs for stability testing of new veterinary drug substances and
551 medicinal products (EMA/CVMP/VICH/581467/2007-VICH GL45)
- 552 • Guideline on Statistical Evaluation of Stability Data (EMA/CVMP/VICH/858875/2011-VICH GL51)
- 553 • Note for guidance on quality of herbal medicinal products / traditional herbal medicinal products
554 (EMA/HMPC/CHMP/CVMP/201116/2005)
- 555 • Note for guidance on specifications: test procedures and acceptance criteria for herbal substances,
556 herbal preparations and herbal medicinal products / traditional herbal medicinal products
557 (EMA/HMPC/CHMP/CVMP/162241/2005)

558 *according to VICH conditions; where appropriate; intermediate storage conditions, if applicable.

559 **Annex I**

560 An active substance is considered as stable if it is within the initial specifications when stored at 25 °C/
561 60% RH or 30°C/65% RH, respectively, (2 years) and 40°C/75 %RH (6 months).

562 **Annex II**

563 **Variations under codes F:**

564 Where the data submitted, long term 25 °C/ 60% RH or 30°C/65% RH, respectively, and accelerated
565 40°C/75% RH or, in case of aqueous products in semi-permeable containers, the respective storage
566 conditions defined in the CVMP Guidelines on Stability Testing of Active Substances and Related
567 Finished Products, show that there is no adverse effect on the stability of the active substance/finished
568 product, the retest period/shelf life originally granted can normally be retained, based on comparison
569 with the original data submitted. However, where the data demonstrate an adverse change in product
570 stability, a new shelf life must be assigned. Based on a case-by-case decision, extrapolation of data
571 may be applied.

572 If real time data are supported by results from studies conducted under accelerated or intermediate
573 storage conditions, the retest period/shelf-life may be extended beyond the end of real time studies.
574 Normally, in those cases in which long-term and accelerated data show little or no change over time
575 and little or no variability the proposed retest period can be extrapolated up to twice but should not be
576 more than 12 months beyond the period covered by long-term data. The degree up to which
577 extrapolation will be acceptable following a change to the active substance or finished product that
578 shows an adverse effect to the stability, will largely depend on the change over time, variability of data
579 observed, proposed storage conditions and extent of statistical analyses performed. It will always have
580 to be a case-by-case decision. For more detailed information on statistical evaluation of stability data
581 please refer to the CVMP/VICH Guideline on Statistical Evaluation of Stability Data.

582 **Variations under codes I:**

583 In case of extrapolation of the retest period of the active substance or of the shelf-life of the finished
584 product beyond available long-term stability data, the principles described in the Guideline on Stability
585 Testing of Existing Active Substances and Related Finished Products (EMA/CVMP/QWP/709423/2022)
586 or the VICH guideline on statistical evaluation of stability data (VICH GL51) should be followed.