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4 Draft guideline on quality and equivalence of topical 5 products

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9 Annexes I and II of this guideline replace Annex 1 of the Guideline on Quality of Transdermal Patches
10 (EMA/CHMP/QWP/608924/2014)

11 The guideline replaces Questions and Answer on Guideline: Clinical Investigation of Corticosteroids
12 Intended for Use on The Skin CHMP/EWP/21441/2006.

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

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Keywords	<i>Medicinal products for cutaneous use, topical products, locally applied locally acting medicinal products, skin permeation, in vitro release, stratum corneum sampling, tape stripping.</i>
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17 Draft Guideline on quality and equivalence of topical 18 products

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77 Executive summary

78 The guideline relates to locally applied and locally acting medicinal products for cutaneous use and is
79 also relevant for other medicines e.g. preparations for auricular or ocular use.

80 Specific guidance is provided:

81 1 On the quality of topical products not covered by other guidelines.

82 2 On equivalence testing of topical products *in lieu* of therapeutic equivalence clinical trials.

83 Existing guidelines state that, for topical products, changes in formulation, dosage form,
84 method of administration or manufacturing process may significantly influence the efficacy
85 and/or safety. Clinical therapeutic equivalence studies are in principle necessary, but other
86 models may be used or developed.

87 Guidance is provided on other models and studies that may be used to independently
88 determine equivalence with respect to (i) quality, (ii) efficacy, and (iii) safety that taken
89 together support a claim of therapeutic equivalence, when the method of administration is the
90 same and risks of inequivalence to the patient are minimal.

91 Guidance is provided on situations where therapeutic equivalence clinical trials will be
92 expected.

93 Scope, limitations and acceptance criteria of this approach are described.

94 The guidance should be used to develop and justify topical product-specific equivalence
95 protocols.

96 In addition, equivalence test protocols are provided for:

- 97 • *in vitro* release
- 98 • *in vitro* human skin permeation
- 99 • *in vivo* stratum corneum sampling (tape stripping)
- 100 • *in vivo* vasoconstriction assay for corticosteroids

101 The quality guidance applies to new marketing authorisation applications and post approval changes.

102 The equivalence guidance is applicable to certain cases of demonstration of equivalence of a new
103 topical medicinal product with an existing medicinal product.

105 1 Introduction and Background

106 The diversity of topical products is very wide given the complex nature of skin, the range of conditions
107 to be treated and the variety of patients and their needs.

108 The guideline cannot present a single procedure to address such diversity, instead general
109 recommendations are provided. These can be applied to any given product on a case-by-case basis.

110 The guideline elaborates existing regulatory guidance and is informed by current scientific knowledge.

111 1.1 *Quality of Topical Products*

112 Guidance on the quality of topical products, not covered by other general quality guidelines, is
113 provided.

114 The indication, target population and site of action need to be understood to enable informed choices
115 with respect to pharmaceutical form, composition, and method of administration.

116 The principal function(s) of the drug product need to be understood. This may simply be administration
117 of the active substance to the surface of the skin. In many cases, bioavailability is increased by
118 including in the product formulation excipients that change the thermodynamic activity of the active
119 substance, e.g. by solubilisation and supersaturation, that modify active substance diffusion, or disrupt
120 the physiological barrier - penetration enhancers. Occlusion and the vehicle itself, e.g. moisturisers and
121 emollients, may influence the condition to be treated.

122 The quality target product profile should consider patient acceptability, ease of removal from the
123 container and administration, bulk aesthetic properties such as appearance, spreadability, feel, the
124 microstructure/physical properties, evaporation of volatile excipients, and occlusion if appropriate.
125 These elements need to be characterised and, when necessary, controlled as critical quality attributes.

126 The product formulation should be developed using sound prior knowledge, established scientific
127 rationale and evidence. The resultant quality characteristics should be determined from multiple
128 batches representative of the product to be marketed.

129 A robust manufacturing process is required to assure consistent product quality through its marketing
130 life-cycle. Marketed products should have the same quality as those batches for which satisfactory
131 evidence of efficacy and safety or equivalence has been demonstrated.

132 Stability is shown when batches at release and at the end of their shelf life have equivalent physical,
133 chemical and microbiological quality characteristics, and includes *in vitro* performance if appropriate.

134 The control strategy should ensure that the product is fit for its intended purpose and complies with
135 relevant pharmacopoeial standards. Inadequate product development or quality cannot be justified by
136 reference to clinical trials.

137 1.2 *Equivalence of Topical Products*

138 Demonstration of equivalence of a new topical medicinal product with an existing medicinal product
139 may be required in the context of marketing authorisation applications relying on the dossier of an
140 existing medicinal product, and in case of product changes during pharmaceutical development or
141 post-approval, which could have a potentially significant impact on the safety, quality or efficacy of the
142 medicinal product.

143 Furthermore in the case of applications which rely on literature to demonstrate the safety and efficacy
144 of the medicinal product the relevance of the literature should be supported by equivalence bridging
145 data between the test product and the product described in the literature. This is because the effect of
146 quality differences in formulation, manufacture and method of administration is not predictable.

147 Existing guidelines state that, for topical products, changes in formulation, dosage form, method of
148 administration or manufacturing process may significantly influence the efficacy and/or safety. Clinical
149 therapeutic equivalence studies are in principle necessary, but other models may be used or developed.

150 This guideline provides further detail on how *in vitro* and *in vivo* models may substitute for clinical data
151 for the purpose of establishing therapeutic equivalence.

152 Demonstration of equivalence with respect to quality is normally not sufficient to predict therapeutic
153 equivalence. In the case of solutions, e.g. cutaneous solutions, a waiver of therapeutic equivalence
154 data may be accepted based on quality equivalence alone, when the method of administration is the
155 same.

156 Equivalence with respect to quality can, where appropriate, be established using comparative data with
157 the comparator medicinal product (i.e. existing medicinal product) comprising pharmaceutical form;
158 qualitative and quantitative composition; microstructure/physical properties; product performance;
159 administration. This is termed "*extended pharmaceutical equivalence*" for the purpose of this guideline.

160 Equivalence with respect to efficacy requires comparative permeation kinetic and, where possible,
161 pharmacodynamic studies with the comparator medicinal product. Suitable permeation kinetic methods
162 are *in vitro* human skin permeation and *in vivo* stratum corneum (S.C.) sampling (tape stripping) of
163 human volunteers and pharmacokinetic bioequivalence. Suitable pharmacodynamic studies include the
164 *in vivo* vasoconstriction assay for corticosteroids and *in vivo* microbial decolonisation studies for
165 antiseptics, undertaken on human volunteers. If permeation kinetics and pharmacodynamic studies are
166 not applicable or are considered insufficiently predictive of clinical response, clinical efficacy data will
167 normally be required.

168 Equivalence with respect to safety and local tolerance may be inferred from knowledge of the active
169 substance and the choice of well-established excipients.

170 Biowaivers from permeation kinetic or pharmacodynamic equivalence studies are described for simple
171 formulations, i.e. in cases where demonstration of equivalence with respect to quality alone would be
172 sufficient.

173 The general guidance should be used to develop product-specific protocols to demonstrate equivalence,
174 facilitated by obtaining scientific advice, as necessary.

175 2 Scope

176 The guideline applies to locally applied and locally acting medicinal products for cutaneous use and
177 may also be relevant for other medicines, e.g. preparations for auricular or ocular use.

178 Guidance is provided on the quality of topical products, containing chemical active substance(s), not
179 covered by other general quality guidelines and on equivalence testing of topical products to support a
180 claim of therapeutic equivalence with comparator medicinal products, *in lieu* of therapeutic equivalence
181 clinical trials.

182 The quality guidance applies to new marketing authorisation applications and post approval changes.

183 The equivalence guidance is applicable to certain cases of demonstration of equivalence of a new
184 topical medicinal product with an existing medicinal product.

185 The equivalence guidance does not apply:

- 186 • To biological medicinal products, see guidelines on similar biological medicinal products.
- 187 • To herbal medicinal products.
- 188 • When equivalence with respect to efficacy is demonstrated by therapeutic equivalence clinical
189 trials.
- 190 • When the pharmaceutical form or qualitative and quantitative composition of the test and
191 comparator products are not the same or equivalent (see section 5.2.1).

192 3 Legal basis

193 This guideline should be read in conjunction with Directive 2001/83/EC and relevant Pharmacopoeial
194 monographs and Guidelines.

195 *Quality Guidelines*

- 196 • Ph. Eur. Dosage Form Monographs: Liquid Preparations for Cutaneous Application; Powders for
197 Cutaneous Application; Semi-Solid Preparations for Cutaneous Application; Ear Preparations; Eye
198 Preparations; Pressurised Pharmaceutical Preparations.
- 199 • Pharmaceutical Development, ICH Q8 (R2), EMEA/CHMP/167068/2004;
- 200 • Manufacture of the Finished Dosage Form, EMA/CHMP/QWP/245074/2015;
- 201 • Guideline on Process Validation for finished products. Information and data to be provided in
202 Regulatory Submissions EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1;
- 203 • Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product
204 CHMP/QWP/396951/06;
- 205 • Q 6A Specifications: Test Procedures and Acceptance Criteria for New Active substances and New
206 Drug Products: Chemical Substances CPMP/ICH/ 367/96-ICH Q6A;
- 207 • Q 2(R1) Validation of Analytical Procedures: Text and Methodology, CPMP/ICH/381/95 - ICH Q2
208 (R1);
- 209 • Stability Testing of New Active substances and Drug Products (ICH Q1A (R2)), CPMP/ICH/2736/99-
210 ICH Q1A (R2);
- 211 • Stability Testing of Existing Active Ingredients and Related Finished Products, CPMP/QWP/122/02
212 Rev. 1 corr.;

213 *Equivalence Guidelines*

- 214 • Note for Guidance on the Clinical Requirements for Locally Applied, Locally Acting Products
215 containing Known Constituents CPMP/EWP/239/95 Final
- 216 • Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr

- 217 • Guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2
- 218 • General Considerations for Clinical Trials (ICH topic E8, CPMP/ICH/291/95)
- 219 • Guideline for Good Clinical Practice (ICH E6 (R1), CPMP/ICH/135/95)
- 220 • Statistical Principles for Clinical Trials (ICH E9, CPMP/ICH/363/96)
- 221 • Reflection Paper on advice to Applicants / Sponsors/ CROs of Bioequivalence Studies
222 EMEA/INS/GCP/468975/2007
- 223 • Reflection paper on statistical methodology for the comparative assessment of quality attributes in
224 drug development Draft (EMA/CHMP/138502/2017). Although a draft document, this paper
225 provides current regulatory considerations regarding statistical aspects for the comparative
226 assessment of quality attributes.
- 227 Equivalence trials conducted using human volunteers in the EU/EEA should be carried out in
228 accordance with Directive 2001/20/EC.
- 229 *In vitro* human skin permeation kinetic equivalence trials, which are pivotal to product approval, are
230 subject to National Competent Authority inspection and should also be carried out in accordance with
231 Directive 2001/20/EC.
- 232 Trials conducted outside of the Union and intended for use in a Marketing Authorisation Application in
233 the EU/EEA should be conducted to the standards set out in Annex I of the community code, Directive
234 2001/83/EC.
- 235 Companies may apply for CHMP and NCA Scientific Advice for specific queries not covered by existing
236 guidelines.

237 4 Quality of Topical Products

238 4.1. Description and composition of the drug product

239 The drug product composition and excipient functions should be described in detail.

240 The names of excipients should be specific and distinct. The recommended international non-
241 proprietary name (INN or INN modified (INNM)) accompanied by the salt if relevant, or the European
242 Pharmacopoeia name, or their usual common name, or the chemical name, otherwise the proposed
243 name should be justified.

244 The name should include the grade or brand (commercial) name, if required for consistent
245 manufacturability and product quality.

246 It should be explicitly stated when an excipient contributes in a multifunctional way to the design and
247 purpose of the drug product, e.g. propylene glycol acting as a humectant, penetration enhancer and
248 solubiliser.

249 The applied dose, in terms of mass of active substance per unit area, based on the SmPC instructions
250 for use, and maximum daily dose, should be stated.

251 The primary packaging and, if necessary, secondary packaging or other materials or components
252 required for reasons of stability or administration, should be described.

253 4.2. *Pharmaceutical development*

254 The pharmaceutical development component of the dossier should form a sound scientific basis for the
255 topical product for its intended use, providing a clear narrative of product development, and include all
256 relevant data.

257 4.2.1. Therapeutic objectives and topical product design

258 The Quality Target Product Profile (QTPP) should identify the intended therapeutic objectives and
259 purpose of the drug product and explain how these objectives are achieved by the product design.

260 A patient-focussed approach should consider: indication and disease state of skin; age
261 appropriateness, patient acceptability, administration and usability, administration site; efficacy in
262 terms of product strength and posology, solute status of the active substance, and bioavailability
263 and/or penetration enhancement; emolliency; safety in terms of ingredient toxicity, impurities,
264 microbial quality; and quality in terms of physical and chemical stability, critical quality attributes and
265 compliance with pharmacopoeial and regulatory requirements.

266 The local site of action should be identified: skin surface; skin interior (stratum corneum, epidermis or
267 dermis); or subcutaneous, adjacent tissues below the skin (regional).

268 The means and permeation kinetics by which the active substance reaches the local site of action
269 should be explained. As applicable, this should address administration, the solution state of the active
270 substance, dissolution, release from the product and diffusion through human skin.

271 In some cases, e.g. skin antiseptic cutaneous solutions, consideration of the method of administration
272 only is appropriate. In others, e.g. NSAID creams, all elements should be considered.

273 The inclusion of excipients to enhance bioavailability and for emolliency should be explained and
274 justified. The choice of formulation, e.g. aqueous gel, cream, ointment, should be explained and
275 justified.

276 If applicable, the proportionality of different strengths should be discussed.

277 Cross references to relevant non-clinical and clinical sections of the dossier should be provided, as
278 appropriate.

279 4.2.2 Active substance (P.2.1.1)

280 Active substance physicochemical properties that are important for bioavailability, the formulation,
281 performance and stability of the drug product should be identified and discussed. Such properties may
282 include molecular weight, partition coefficient, melting point (boiling point if applicable), pKa,
283 sensitivity to light, air or moisture, degradation pathway, solubility and pH effects, as well as particle
284 size and polymorphism, if the active substance is present in the solid state in the drug product. Critical
285 quality attributes should be identified and controlled in the Drug Substance Specification.

286 4.2.3 Excipients (P.2.1.2)

287 Excipients used in topical products often show batch and source variation e.g. homologue composition
288 of hydrocarbon chains, the degree of unsaturation, molecular weight, polymorphism. This in turn may
289 lead to unforeseen variability in the product rheological properties, microstructure/physical properties,
290 crystallisation of the active substance or other ingredient, stability, or bioavailability.

291 Batch and source variation of excipients should be considered and addressed during development.
292 The choice and quantity of each excipient, and relevant critical quality attributes (CQAs), should be
293 discussed and justified in relation to its function(s), including an emollient function, if applicable.
294 The grade of the excipient should be specified, when active substance bioavailability, product
295 manufacturability and / or quality is altered if other grades are used.
296 CQAs of the excipients should be controlled in their specifications and their limits justified (P.4.).
297 Detailed information on those excipients which might have an influence on the active substance
298 permeation and bioavailability, e.g. solubiliser, penetration enhancer, should be provided, including
299 their ability to provide their intended function and to perform throughout the intended drug product
300 shelf life.
301 In the case of excipients presented as a mixture of compounds, details of the composition should be
302 provided in qualitative and quantitative terms and characterised, including rheological properties if
303 appropriate.
304 For novel excipients, full details of manufacture, characterisation and controls with cross references to
305 supporting safety data should be provided.
306 For excipients also used in cosmetics, data showing compliance with Regulation 1223/2009 on
307 Cosmetic Products, would be supportive.
308 Processing aids should be identified and described.
309 Some excipients traditionally used in topical products may cause irritation or sensitivity reactions and
310 should if possible be avoided, or minimised if unavoidable, in the development of a new product. For
311 reference, see the guideline on "Excipients in the label and package leaflet of medicinal products for
312 human use".

313 4.2.4. Formulation development

314 The development of the drug product should be described with respect to the defined QTPP, employing
315 suitable tests to characterise and control CQAs, factors affecting ease of administration and duration of
316 use, and product performance e.g. dissolution, *in vitro* drug release and if appropriate *in vitro* skin
317 permeation. Evidence of the suitability of the test methods and acceptance criteria used to assess the
318 product should be provided (see also Annexes I and II).

319 The presentation of the active substance in the drug product e.g. as a solute or in a suspension, and
320 the degree of saturation are CQAs, which should be justified in terms of product efficacy and safety,
321 supported by evidence of how the target state is achieved during manufacture and maintained during
322 storage.

323 The risks of precipitation / particle growth / change in crystal habit, or changes to other active
324 substance characteristics likely to affect bioavailability, arising from changes in temperature and on
325 storage should be assessed and appropriate tests included in the stability studies.

326 The delivery of the active substance to the site of action needs to be discussed. Solvents and
327 enhancers can be used to aid transport through the different layers of the skin. Ointments may
328 function to occlude the skin and thus facilitate permeation. The concentration gradient of the active
329 substance between the drug product and the site of action is a driving force for delivery and achieving
330 a saturated status of the active substance in the drug product can therefore be crucial.

331 Patient acceptability and usability of the drug product should be considered e.g. ease of administration,
332 spreadability, which can be of importance for dose per surface area, and feel (dry or greasy).

333 Where appropriate, the type of the pharmaceutical form should be identified e.g. hydrophobic ointment
334 (hydrocarbon base, absorption base), water emulsifying ointment, hydrophilic ointment.

335 Product microstructure/physical properties, which may be complex for semisolid products, and
336 mechanisms responsible for its formation during processing, should be understood e.g. in terms of
337 excipient interactions, batch variation and scale-up, so that the manufacturing process can be
338 optimised to give a consistent quality product.

339 Transformation of the topical product on administration should be discussed. Particularly in those cases
340 where evaporation of volatile solvents and excipients, or other phenomena, are necessary for effective
341 drug delivery to the site of action.

342 The clinical trial formulation and the batches used in the comparative studies should be described in
343 detail. Any differences in formulation and manufacturing processes between pivotal clinical batches and
344 the drug product to be marketed should be justified. Results from comparative extended
345 pharmaceutical equivalence studies, *in vitro* studies or *in vivo* studies should be provided.

346 When the formulation composition is decided, up-scaling of the manufacturing process will start and
347 the critical process parameters should be identified and controlled.

348 During this period, it is reasonable to expect that necessary adjustments will be made to reach and
349 optimise full-scale production. These adjustments might be changes in composition, manufacturing
350 processes, equipment or manufacturing site. In some cases, the potential impact of these adjustments
351 on the functions of the drug product, e.g. with respect to bioavailability and usability, should be
352 assessed.

353 Evidence of compliance with Ph. Eur. requirements for the topical dosage form should be provided.

354 The relationship between the QTPP, critical quality attributes and the drug product specification should
355 be fully discussed.

356 Where the drug product vehicle contains flammable volatile solvents, e.g. isopropyl alcohol and
357 ethanol, the flash point should be determined in compliance with relevant ISO standards and
358 appropriate warnings included in the product information (see also section 4.2.6).

359 Drug products with a paraffin vehicle are not in themselves flammable, but when clothing, bedding and
360 dressings become impregnated with these, the material acts as a wick and the paraffin acts as an
361 accelerant when ignited. The patient risks should be assessed, and appropriate warnings included in
362 the product information (see also section 4.2.6).

363 4.2.5 Product characterisation

364 A detailed product characterisation should be developed to facilitate life-cycle management and, where
365 applicable, to support a claim of equivalence to original or comparator medicinal products.

366 Characterisation data should be derived from a representative number of batches taking account of the
367 likely variation seen with disperse systems compared with simple solutions, and should not be less
368 than three batches.

369 To enable statistical evaluation, the number of samples should be representative, with at least 12 units
370 per batch for each experiment. Between batch variability e.g. due to batch size, date of manufacture
371 and period of storage, should also be taken into account.

372 *Pharmaceutical Form*

373 The diverse topical dosage forms include cutaneous solutions, foams and sprays, shampoos, ointments
374 (hydrocarbon, absorption, water-removable and water-soluble bases), creams (oil in water or water in
375 oil), gels, pastes, poultices, medicated plasters and cutaneous patches.

376 Evidence should be provided that characterises the pharmaceutical form in terms of the solution state
377 of the active substance, disperse and immiscible phases and dosage form type.

378 For example:

379 Active substance in solution, single phase vehicle: e.g. cutaneous solution, single phase gel or
380 ointment.

381 Active substance in suspension, single phase: e.g. cutaneous suspension.

382 Active substance in solution, two phase vehicle: e.g. o/w cream, active substance in solution in oily
383 phase.

384 Active substance in suspension, two phase vehicle: e.g. o/w cream, active substance insoluble in either
385 phase in suspension.

386 For suspensions, additional characterisation in terms of active substance particle size distribution and
387 polymorphic form, including photomicrographs, is required.

388 For immiscible phase formulations, additional characterisation in terms of globule size distribution and
389 appearance, including photomicrographs, is required.

390 Particle size analysis by diverse methodologies should be employed, if possible e.g. laser light
391 diffraction, Raman chemical imaging, as well as microscopy.

392 *Appearance*

393 This should be characterised visually and with microphotography - particularly for dispersed systems.

394 *Microstructure / Physical Properties*

395 Evidence should be provided to characterise the microstructure/physical properties in terms of bulk
396 physical CQAs that influence bioavailability, usability or indicate variability in the manufacturing
397 process and product instability.

398 e.g. for solutions and suspensions – pH, buffering capacity, viscosity, density, surface tension,
399 osmolality.

400 e.g. for semisolid formulations – pH, density, rheological behaviour.

401 Non-Newtonian rheological behaviour should be characterised using an appropriate absolute rheometer
402 and include:

- 403 • A complete flow curve of shear stress (or viscosity) versus shear rate, comprising multiple data
404 points across the range of increasing and decreasing shear rates so that any linear portions of
405 the up-curves or down-curves are clearly identified. The resulting curves should be

406 characterised by fitting to (modified) power law equations so that numerical data can be
407 produced.

408 • Yield stress and creep testing

409 • The linear viscoelastic response (storage and loss modulus vs. frequency)

410 Rheograms should be provided and the product's behaviour classified according to shear and time
411 effects e.g. pseudoplastic, dilatant, thixotropic, and characterised using appropriate metrics. For
412 example: viscosities at specified shear rates across the rheograms (e.g. η_{100}); plastic flow yield stress
413 values; thixotropic relative area (S_R); viscoelastic storage and loss moduli (G' and G''), apparent
414 viscosity, loss tangent ($\tan \delta$).

415 Appropriate characterisation of rheological properties may enable the identification or design of a
416 simpler test to be used in the Finished Product Specification.

417 *Product Performance*

418 Appropriate tests to characterise product performance such as dissolution of suspensions and *in vitro*
419 drug release (Annex I) should be developed and shown to be stable during storage.

420 *In vitro* skin permeation (Annex II) testing may also be of value.

421 4.2.6 Administration

422 The SmPC and product information should include instructions for use and any necessary warnings for
423 the safe use of the drug product.

424 Where relevant, transformation of the drug product on administration should be described.

425 The following should be considered:

426 Site of administration;

427 The necessity to avoid damaged or undamaged skin;

428 The requirements for skin pre-treatment;

429 Effect of exposure to environmental extremes of heat, cold, sunlight;

430 Effect of normal human behaviour such as washing, showers, use of sun screens and moisturisers;

431 Any necessary restrictions e.g. avoidance of occlusion;

432 The practical suitability of any special storage conditions;

433 Avoiding inadvertent use by children;

434 For drug products containing flammable volatile solvents, appropriate flammability safety warnings.

435 For example:

436 *Danger: Flammable.*

437 *Keep away from heat, hot surfaces, sparks, open flames and other ignition sources.*

438 *No smoking. Protect from sunlight.*

439 *Do not expose to temperatures exceeding 50°C.*

440 *Do not spray on flames or other sources of ignition.*

441 Patients being dispensed or treated with large quantities (> 100g) of any paraffin-based product
442 should be advised to regularly change clothing, bedding or dressings impregnated with the product
443 and keep away from naked flames.

444 For example:

445 *When this paraffin-based product is covered by a dressing or clothing, there is a danger that*
446 *smoking, or using a naked flame could cause your dressing or clothing to catch fire.*

447 *Do not smoke, use naked flames (or be near people who are smoking or using naked flames) or*
448 *go near to anything else which may cause a fire whilst these products are in contact with your*
449 *clothes, dressing or bandages.*

450 *Ensure that your clothes and bedding are changed regularly (preferably daily) as the paraffin*
451 *soaks into the fabrics and can potentially be a fire hazard. You should also be careful to make sure*
452 *that the paraffin does not soak into chairs, seating or other furniture.*

453 *Tell your relatives or carers about your treatment and show them this leaflet.*

454 *Tell your doctor, nurse or pharmacist if you normally smoke. They will be able to offer you help*
455 *and advice to stop smoking.*

456 4.2.7 Manufacturing process development and Manufacture (P.2.3 457 and P.3)

458 For dispersed drug products, e.g. two-phase emulsions, changes in formulation or manufacturing
459 process may influence the efficacy and/or safety of the product and are therefore important to
460 evaluate and control. The order of addition of different components to the formulation can be of
461 importance as well as process parameters such as temperature and homogenisation conditions e.g.
462 speed and duration.

463 In a typical manufacturing process, the critical points are generally the formation of a two- or multi-
464 phase system from one-phase systems and the point at which the active substance is added.

465 As the drug release rate, microstructure/physical properties and rheological profiles of the drug
466 product may be susceptible to scale-up effects, it is particularly important that these properties are
467 verified at the commercial scale.

468 Module 3.2.P.3.3 and 3.2.P.3.4 should be sufficiently detailed and include both critical and non-critical
469 process parameters and justified by reference to the manufacturing process development undertaken.

470 Hold times and storage conditions of different solutions and intermediate materials should be stated
471 and justified, supported by appropriate stability studies and other relevant data.

472 Many bulk topical products exhibit shear thickening in the days following manufacture. The time
473 between product manufacture and assembly may need to be optimised.

474 The suitability of the packaging for intermediates, bulk storage, and transportation (shipping) should
475 also be discussed.

476 4.2.8 Container closure system (P.2.4)

477 The suitability of the container closure system (described in 3.2.P.7) should be discussed and justified.
478 This should include the choice of materials, protection from moisture, oxygen and light where
479 applicable, drug product compatibility, dosing, usability and safety.

480 Drug products having sterile requirements should be packaged in single-use containers.

481 If any device is co-packaged to facilitate e.g. the measuring or application of the product, the device
482 should be CE-marked. Compatibility between the device and the medicinal product should be shown
483 and if it is a measuring device, the dose accuracy should be demonstrated with the applied product.

484 4.2.9 Microbiological Attributes (P.2.5)

485 Microbiological aspects should be considered in the same manner as for other administration routes,
486 bearing in mind that cutaneous products are sometimes applied to damaged skin. Reference should be
487 made to European Pharmacopoeia 5.1.4., Microbiological quality of non-sterile pharmaceutical
488 preparations.

489 Sterility of the drug product is required if it is to be used on large open or deep wounds or on severely
490 injured skin, and products used prior to invasive procedures (e.g. preoperative skin antiseptic) and for
491 preparations for irrigation.

492 For non-sterile drug products in multiple-use containers the need to include an antimicrobial
493 preservative should be addressed and justified. The concentration used should be at the lowest feasible
494 level. Reference should be made to European Pharmacopoeia 5.1.3., Efficacy of antimicrobial
495 preservation. For multi-phase formulations, the solubility of the preservative in the different phases
496 needs to be considered.

497 4.3 Control strategy

498 General regulatory guidance on the establishment and justification of a control strategy for the drug
499 product is given in other relevant guidelines, including ICH Q8, Q9, and Q10. Attention should however
500 be paid to the control of CQAs required for the control of drug release, i.e. the *in vitro* drug release /
501 dissolution and, if appropriate *in vitro* skin permeation.

502 If possible, pharmaceutical development should establish the link between product performance quality
503 attributes and clinical efficacy.

504 4.3.1 Drug product specification (P.5)

505 General guidance on the drug product specification is given in ICH Q6A, Q3B, Q3C and Q3D and the
506 European Pharmacopoeia lists dosage form monographs.

507 The drug product specification should contain tests for the physical, chemical and microbiological
508 quality, and product performance i.e. the established product characteristics (see 4.2.5) are controlled.

509 Crystal formation is a quality deficiency likely to adversely influence efficacy. Syneresis, the extraction
510 or expulsion of a liquid from a semisolid, is another deficiency. Uniformity of the finished product in the
511 container should be considered to detect sedimentation phenomena.

512 For topical products, the calculation of maximum daily dose for limits for degradation products is not as
513 straightforward as for solid oral preparations or injections. The duration of treatment and amount
514 required is usually more varied. The exposure levels from cutaneous products can usually be
515 considered much less than from routes with systemic exposure. Deviations from standard calculations
516 should be justified from a safety perspective.

517 Specific precautions in calculating acceptance limits for impurities should be made for cutaneous
518 products applied to damaged skin or products containing penetration enhancers.

519 Limits for performance tests, i.e. dissolution, drug release using a synthetic membrane and, if
520 appropriate skin permeation testing, if included in the specification should be justified by reference to
521 clinical batches for which satisfactory efficacy and safety has been demonstrated. The limits should be
522 the same at release and shelf life, unless justified and qualified by clinical data.

523 4.4 *Stability program (P.8)*

524 To assure quality and stable product characteristics throughout storage, the designated shelf life needs
525 to be based on physical, chemical and microbiological stability, and *in vitro* release or other
526 performance tests.

527 The risk factors to product stability should be assessed e.g. precipitation, particle growth, change in
528 crystal habit, or other active substance characteristics likely to affect the thermodynamic activity,
529 changes in emulsion characteristics. Appropriate tests, additional to those in the product specification,
530 should be included in the drug product stability study quality specification.

531 Shear thickening and changes in the product microstructure are also risk factors that should be
532 considered.

533 The stability programme should include stress testing to assess the effect of severe conditions on the
534 drug product e.g. temperature cycling for creams and emulsions.

535 The stability study quality specification should include tests to monitor the suitability of the container
536 closure system.

537 Requirements for special storage conditions e.g. do not refrigerate, should be addressed.

538 An in-use stability programme should be undertaken. It is important that these tests have a
539 reasonable length considering dosage regimen and package size. Unnecessary wastage or too short in-
540 use shelf-lives should not be proposed.

541 5 Equivalence of Topical Products

542 5.1 *Scope*

543 This section addresses equivalence testing of topical products to support a claim of therapeutic
544 equivalence with comparator medicinal products, *in lieu* of therapeutic equivalence clinical trials.
545 Aspects relating to quality, efficacy, and safety are discussed.

546

547 For simple formulations (e.g. single-phase solutions, gels, ointments) demonstration of equivalence
548 with respect to quality, i.e. extended pharmaceutical equivalence, may be sufficient.

549 For more complex formulations, or those containing excipients that might directly influence the active
550 substance bioavailability or product performance, then additional permeation kinetic and, if possible,
551 pharmacodynamic equivalence tests are normally required.

552 The formulation and strength of the drug product must also be such that the equivalence tests and
553 associated analytical methods are sufficiently sensitive, discriminating, accurate and precise to
554 measure a quantifiable permeation kinetic or pharmacodynamic event.

555 This approach is not applicable and clinical therapeutic equivalence studies are in principle required for
556 the following drug products:

- 557 • With a narrow therapeutic index.
- 558 • With dose related, systemic toxicity, except in those cases where equivalent systemic exposure
559 is shown by conventional pharmacokinetic bioequivalence studies.
- 560 • Where the means e.g. dissolution, release, diffusion, and permeation kinetics by which the
561 active substance reaches the local site of action is not established or understood.
- 562 • Where the method of administration is not the same.
- 563 • That cannot be fully characterised with respect to quality attributes e.g. due to complex
564 formulation, methodological limitations.
- 565 • Where it is not possible to measure a quantifiable permeation kinetic or pharmacodynamic
566 event e.g. due to limited diffusion or insensitive tests.
- 567 • Where *in vitro* and *in vivo* permeation kinetic and pharmacodynamic studies are not applicable
568 or considered insufficiently predictive of clinical response e.g. products indicated for the
569 treatment of open wounds and ulcers.

570 5.2 *Equivalence with respect to quality (extended pharmaceutical* 571 *equivalence)*

572 Equivalence requires comparative quality data with the relevant comparator medicinal product. The
573 products should be characterised (see sections 4.2.5 and 5.5).

574 Pharmaceutical form, qualitative and quantitative composition, microstructure/physical properties,
575 product performance e.g. dissolution, *in vitro* release test, and method of administration should be
576 compared. For volatile solvent based topical products, product transformation on administration should
577 also be compared.

578 Product quality equivalence should be undertaken on batches representative of the product to be
579 marketed and the manufacturing process – i.e. batches at or near production scale. Alternatively, pilot
580 scale batches, at least 1/10 production scale may be used for characterisation and comparative
581 purposes, if there are no changes in the manufacturing process and equipment, and evidence provided
582 that scale-up does not affect product quality.

583 It is acknowledged that there may be only a limited number of representative batches available at the
584 time of submission, and at least three different batches of both the test and comparator products
585 should be compared.

586 To enable statistical evaluation, the number of samples should be at least 12 units per batch for each
587 experiment.

588 Data are also required to show that the product characteristics remain consistent and equivalent
589 throughout the designated shelf-life.

590 5.2.1 Extended pharmaceutical equivalence acceptance criteria

591 The extended pharmaceutical equivalence acceptance criteria between the test and comparator
592 medicinal product are:

593 *Pharmaceutical form*

- 594 • The drug product should be the same pharmaceutical form, with the same solution state of the
595 active substance in the same immiscible phases.

596 *Qualitative and Quantitative Composition*

- 597 • The active substance content, and its salt form should be the same.

- 598 • In general, the excipients qualitative composition, including grade, if necessary, and
599 quantitative composition of excipients should be the same, although some exceptions are
600 permitted.

601 In particular, excipients whose function is to influence the active substance solubility,
602 thermodynamic activity or bioavailability and product performance should be qualitatively the
603 same.

604 The nominal quantitative composition of the excipients should be the same or differences not
605 greater than $\pm 5\%$. For example, for an excipient present in the comparator medicinal product
606 at 2%w/w, the permitted range in the test product is 1.9 – 2.1%w/w.

- 607 • A permitted exception for a *qualitatively* different excipient may be acceptable for:
 - 608 • Excipients whose primary function is not related to product performance or
609 administration, i.e. antioxidants, antimicrobial preservatives, colours, and do not have
610 any other functions or effect that influences the active substance solubility,
611 thermodynamic activity or bioavailability and product performance.

612 Well-established excipients in usual amounts should be employed and possible
613 interactions affecting drug bioavailability and/or solubility characteristics should be
614 considered and discussed.

- 615 • Excipient paraffin homologues may be acceptable for excipients whose function relates
616 to the vehicle or emolliency, and do not influence the active substance solubility,
617 thermodynamic activity or bioavailability and product performance.

618 The different excipient should have no effect on local tolerance or safety. It should be shown
619 that the excipients do not have any other functions or effect that influences the active
620 substance solubility, thermodynamic activity or bioavailability and product performance. In
621 these cases, a bio waiver (section 5.5.1) cannot be justified and is not permitted.

- 622 • A permitted exception for a *quantitative* difference of not greater than $\pm 10\%$ is acceptable:
 - 623 • For excipients whose function only relates to the vehicle properties or emolliency.
 - 624 • For excipients whose function is not related to product performance or administration,
625 i.e. antioxidants, antimicrobial preservatives, colours.

626 It should be shown that the excipients do not have any other functions or effect that influences
627 the active substance solubility, thermodynamic activity or bioavailability and product
628 performance.

629 *Acceptance Criteria*

- 630 • For quantitative quality characteristics, the 90% confidence interval for the difference of means
631 of the test and comparator products should be contained within the acceptance criteria of +/-
632 10% of the comparator product mean, assuming normal distribution of data.
- 633 • Qualitative quality characteristics should be essentially the same.

634 *Administration*

- 635 • The method of administration and administration devices should be similar and achieve the
636 same dose on application.
- 637 • If applicable, when product transformation occurs following administration, the test and
638 comparator medicinal product residues are equivalent with respect to quality i.e. in terms of
639 extended pharmaceutical equivalence.

640 *5.3 Equivalence with respect to efficacy*

641 *5.3.1 Methods*

642 The following methods are considered suitable for equivalence testing, *in lieu* of a clinical therapeutic
643 study:

644 *Permeation Kinetics Studies*

- 645 • *In vitro* skin permeation
- 646 • Stratum Corneum Sampling (Tape Stripping)
- 647 • Pharmacokinetic bioequivalence

648 These tests provide a means of measuring equivalence in active substance permeation kinetics of drug
649 products applied to intact skin.

650 Human bioequivalence studies are appropriate when the active substance has quantifiable systemic
651 bioavailability. *In vitro* skin permeation studies are suitable when the active substance diffuses through
652 the skin to permit quantification in the receptor cell. Stratum Corneum Sampling (Tape Stripping) is
653 suitable when there is sufficient quantifiable drug diffusion across the stratum corneum.

654 Other techniques, such as Microdialysis and Confocal Raman spectroscopy are not sufficiently
655 established to provide pivotal equivalence data but may be supportive.

656 *Pharmacodynamic Studies*

- 657 • Vasoconstriction Assay for corticosteroids.
- 658 • Antiseptic and anti-infective studies.

659 These studies provide a means of measuring equivalence in active substance pharmacodynamic
660 activity of drug products applied to intact skin.

661 Pharmacodynamic studies for other drugs are not sufficiently established to provide pivotal equivalence
662 data but may be supportive. The model should be suitably valid and its relationship with the
663 therapeutic situation must be demonstrated.

664 5.3.2 General Considerations

665 *Managing Variability*

666 The test conditions should be standardised to minimise the variability of all factors involved except
667 those of the products being tested. Pilot studies are recommended to develop and optimise
668 procedures.

669 Because the studies are single-dose, product application is a significant source of variability. The dose
670 application procedure (and removal procedure for stratum corneum sampling (tape stripping)) should
671 be practical and carefully described, in accordance with the SmPC of the comparator product, and
672 strictly controlled, e.g. use of administration templates or aids by a single or limited number of trained
673 personnel. The procedure should enable determination of the actual dose applied. The procedure
674 should be validated.

675 The study duration should be sufficient to permit quantitative observation of diffusion, but optimally
676 limited to minimise changes in test conditions that may naturally occur, which introduce bias to kinetic
677 profiles, e.g. desquamation, loss in skin integrity, back diffusion, accidental loss or transfer of applied
678 dose.

679 The methods involve multiple complex steps. The studies should be conducted following strict protocols
680 by experienced trained staff, with quality assurance in place.

681 *In vitro* skin permeation and stratum corneum sampling (tape stripping) studies should include
682 negative controls that are not equivalent to the test and comparator products.

683 Inter-subject or inter-donor skin variability should be minimised by a cross-over study design.

684 For *in vitro* skin permeation and stratum corneum sampling (tape stripping) studies, the test,
685 comparator and negative control formulations should each be tested on the same set of volunteers or
686 donor skin.

687 For low strength and limited diffusion drug products, the very low active substance concentrations
688 expected in samples may be a significant source of variability. Sensitive analytical methods should be
689 used, e.g. coupled chromatography – mass spectroscopy systems.

690 The analytical methods should comply with the Guideline on bioanalytical method validation.

691 *Dose*

692 The dose, in terms of (a) mass of active substance, (b) application area, and (c) mass or volume of
693 drug product used, should be specified and based on the comparator product SmPC instructions for
694 use.

695 The application area should be at least sufficient to achieve quantifiable results. If necessary, the area
696 may be greater than normally indicated, if without safety concerns.

697 For *in vivo* studies, the skin site should be justified.

698 *Sample sizes*

699 The number of human volunteer subjects should be based on an appropriate sample size calculation
700 and not less than 12.

701 For *in vitro* skin permeation studies, the number of donors may be less than 12, if justified.

702 For *in vitro* skin permeation and stratum corneum sampling (tape stripping) studies, a replicate design
703 is required. The minimum number of experiments for each of the test, comparator and control
704 products should not be less than 24.

705 The number and frequency of sample time points, per subject or replicate, should be sufficient to
706 characterise the active substance kinetic profile and determine equivalence parameters.

707 *Acceptance Criteria*

708 The acceptance criteria for equivalence parameters is that the 90% confidence interval for the ratio of
709 means of the test and comparator products should be contained within the acceptance interval of
710 80.00- 125.00%, unless justified.

711 Wider acceptance criteria for the 90% confidence interval, to a maximum of 69.84 – 143.19, may be
712 accepted in the case of high within-subject or within-donor variability observed with low strength and
713 limited diffusion drug products, and if clinically justified. The procedure in the Guideline on
714 Investigation of Bioequivalence, “Section 4.1.10 Highly variable drugs or drug products” should be
715 followed.

716 *Accreditation*

717 It should be ensured that the performing laboratory is qualified to undertake the studies and that an
718 effective quality system is in place. This should include:

- 719 • A declaration of compliance with a suitable quality system.
- 720 • The technical ability of the performing laboratory and the validity of the method used should be
721 internally assessed at regular intervals and recent results provided;
- 722 • External audit by a National Competent Authority.

723 5.3.3 Permeation Kinetic Studies

724 Specific guidance for each of the three methods is available:

- 725 • *In vitro* skin permeation (Annex II of this guideline)
- 726 • Stratum Corneum Sampling (Tape Stripping) (Annex III of this guideline)
- 727 • Bioequivalence Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1)

728 5.3.4 Pharmacodynamic Studies

729 Corticosteroids

730 The vasoconstriction assay for corticosteroids is accepted for equivalence testing.

731 The study should comply with the methodology described in Annex IV.

732 Skin Antiseptics

733 Skin antiseptics should comply with Ph Eur 5.1.11. *Determination of bactericidal, fungicidal or*
734 *yeastocidal activity of antiseptic medicinal products.*

735 Where the method of administration is poorly defined or new then *in vivo* volunteer tests should be
736 undertaken. In these studies, volunteer's indigenous flora are recovered before and after skin
737 antiseptics, with justified criteria for microbial recovery log reduction.

738 For skin antiseptics for use prior to invasive procedures, a study in compliance with ATSM E1173 – 15
739 *Standard Test Method for Evaluation of Pre-operative, Pre-catheterization, or Pre-injection Skin*
740 *Preparations* would be acceptable.

741 Antimicrobial drug products for treatment of skin infections

742 *In vitro* skin infection and decolonisation equivalence studies, if satisfactorily validated, may be
743 acceptable to provide an assurance of equivalence in efficacy, in conjunction with other equivalence
744 studies.

745 5.4 *Equivalence with respect to safety*

746 In general, safety and local tolerance may be guaranteed by knowledge of the active substance and
747 the choice of well-established excipients.

748 Equivalence with respect to quality, when shown, provides an assurance of safety and local tolerance.

749 In addition, equivalence seen with permeation kinetic equivalence studies would show that the same
750 amount of active substance is expected to reach the site of action and/or the systemic circulation as
751 the comparator medicinal product.

752 For topical products, with a regional site of action, where the active substance has systemic
753 bioavailability, bioequivalence studies provide evidence of both efficacy and safety.

754 As discussed in section 5.1, drugs with dose related, systemic toxicity are out of scope and require
755 local tolerance and clinical safety studies. However, if systemic exposure is measurable, a
756 bioequivalence study showing a similar systemic pharmacokinetic profile would be sufficient to
757 conclude that systemic exposure is not higher for the test product than for the comparator product.

758 5.5 *Topical Product Specific Equivalence Protocols*

759 The development of topical product specific equivalence protocols and choice of equivalence tests
760 should consider the following key factors: pharmaceutical form; product formulation; drug dissolution
761 and release; drug diffusion in the skin and site of action.

762 A formal topical product specific equivalence protocol, with test methods and their acceptance criteria,
763 should be provided and justified. The protocol should be prepared before commencing the equivalence
764 studies. All data available, positive and negative, should be provided.

765 Equivalence may be concluded if results comply with the protocol criteria specified *a priori*.

766 In general, the product-specific equivalence protocol should comprise:

- 767 • Justification for the absence of a clinical therapeutic equivalence study; that the drug product
768 is within and not out of the scope of this guideline (Section 5.1).
- 769 • Justification for the absence of safety studies (section 5.4).

- 770 • Extended pharmaceutical equivalence studies and equivalence in the method of administration
771 (Section 5.2).
- 772 • An appropriate permeation kinetic equivalence study, if diffusion through the skin is relevant to
773 efficacy (Section 5.3.3) and justification of the choice of study or studies. Alternatively, if
774 applicable, justification for the absence of kinetic equivalence studies.
- 775 • Pharmacodynamic studies should also be performed, if possible and relevant. The development,
776 validation and conduct of novel studies is encouraged (Section 5.3.4).

777 5.5.1 Biowaivers

778 A waiver of the need to provide permeation kinetic or pharmacodynamic equivalence data can in
779 principle be acceptable for:

- 780 • Simple formulations with a single-phase base in which the active substance is in solution or
781 suspension e.g. cutaneous solutions, single phase gels and ointments; cutaneous suspensions.
- 782 • If the objectives and purpose of the drug product is only administration of the active substance
783 to the surface of the skin (see section 4.2.1), then extended pharmaceutical equivalence,
784 including *in vitro* drug release for gels, ointments and suspensions, and equivalence in
785 administration should normally be sufficient

786 Equivalence studies with respect to efficacy (Section 5.3) are *always* required if the formulation:

- 787 • Includes excipients whose function is to influence the active substance bioavailability, product
788 performance or enhance drug penetration;
- 789 • Includes complex excipients where different suppliers or grades may affect the *in vivo*
790 performance or stability of the active substance;
- 791 • Has a *qualitatively* different excipient composition from the comparator product (see section
792 5.2.1, Qualitative and Quantitative Composition, line 568).

793 Bioequivalence studies should usually be provided if the products have a regional site of action, where
794 the active substance has quantifiable systemic bioavailability.

795 5.5.2 Strength Biowaiver

796 If several strengths of a test product are applied for, it may be sufficient to establish equivalence at
797 only one strength, which is most sensitive to detect potential differences between formulations.

798 The following requirements must all be met where a waiver for additional strength(s) is claimed:

- 799 a) the different strengths of the test products are manufactured by the same manufacturing
800 process.
- 801 b) the different strengths of the test products have the same qualitative composition.
- 802 c) the qualitative and quantitative compositions of the different strengths of the test products are
803 equivalent to the different strengths of the comparator medicinal products.
- 804 d) extended pharmaceutical equivalence (section 5.2) is demonstrated between the test and
805 comparator medicinal product for all strengths.

806 6 Post-authorisation changes

807 For any proposed change, a risk assessment should be performed to determine its impact on quality,
808 safety, or efficacy of the product.

809 Risks arising from cumulation of changes from the original drug product should also be considered.

810 The following changes are considered to have a potential significant impact on the safety, quality or
811 efficacy of the drug product:

- 812 • A change in the physicochemical state and / or thermodynamic activity of the active
813 substance;
- 814 • A change that affects dissolution, *in vitro* release, *in vitro* permeation kinetic characteristics of
815 the drug product.
- 816 • A change in the manufacturing process e.g. a change in a critical process parameter.

817 The comparative medicinal product for use in equivalence studies is usually that authorised under the
818 currently registered formulation, manufacturing process, packaging etc.

819 If the proposed change meets the extended pharmaceutical equivalence acceptance criteria (section
820 5.2.1) for pharmaceutical form, and qualitative and quantitative composition, then equivalence should
821 be demonstrated according to this guideline using a product specific equivalence protocol, with justified
822 test methods and acceptance criteria (section 5.5).

823 If the proposed change does not meet the extended pharmaceutical equivalence acceptance criteria
824 (section 5.2.1) for pharmaceutical form, or qualitative and quantitative composition, then equivalence
825 should be demonstrated using an appropriate clinical study.

826 In all cases, the change should be supported by appropriate and representative batch data of the
827 original and proposed change of all critical quality attributes.

829 Annex I In vitro release test (IVRT)

830 1. Scope of IVRT

831 This annex provides information for *in vitro* release test (IVRT) of semisolid drug products (e.g. creams,
832 gels or ointments) and liquid suspensions.

833 The following types of topical products are out scope for IVRT, but other *in vitro* tests may be
834 applicable: simple liquid solutions, topical powders and other non-standard topical formulations (such
835 as foams).

836 2. Rationale for IVRT

837 An IVRT with pseudo-infinite dosing using diffusion cells evaluates the rate and extent of release of an
838 active substance in the proposed formulation.

839 The following parameters should be determined:

- 840 • Drug release rate (R): The slope of the cumulative amount of active substance released versus
841 the square root of time for the linear portion of the drug release profile. If a linear portion of
842 the drug release profile cannot be obtained, the IVRT is not valid.
- 843 • The cumulative amount (A) of active substance released, usually expressed in mass units per
844 surface area, at the last sampling time of the linear portion.
- 845 • Lag time (if present)

846 Although the test does not model *in vivo* performance, the release rate (R) is a CQA to be specified in
847 the finished product release and shelf life specification, unless otherwise justified.

848 The *in vitro* release limits should be justified by reference to the *in vitro* release observed with clinical
849 batches for which satisfactory efficacy or equivalence has been demonstrated.

850 Release and shelf life limits should normally be the same, unless the reasons for the differences are
851 satisfactorily explained on quality grounds and justified by reference to clinical batches, and tighter
852 limits at release are set, to ensure that the product will remain within the shelf life specification.

853 A validated *in vitro* release test is required to support extended pharmaceutical equivalence.

854 3. Study design

855 A pilot IVRT study comparing the test and comparator products is recommended to confirm the
856 suitability of the chosen membrane and to validate the experimental conditions.

857 The experimental conditions should be justified with respect to the following:

858 a. Choice of membrane:

859 i. The membrane should ensure that the product and the receptor medium remain separate to
860 ensure the tested formulation remains unchanged throughout the testing period.

861 The membrane should not be rate-limiting to active substance release.

- 862 ii. The membrane should be compatible with the drug product formulation and not bind to the
863 active substance.
- 864 b. Choice of receptor medium:
- 865 i. Sink conditions should be confirmed. An acceptable sink condition is one where the maximum
866 concentration of the active substance in the receptor medium achieved during the experiment
867 does not exceed 30% of its maximum solubility in the receptor medium. **Sink conditions**
868 **normally occur in a volume of medium that is at least 3-10 times the saturation volume.**
- 869 ii. Back diffusion of the receptor medium should be minimised to avoid transformation of the
870 applied drug product. The pH of the receptor medium should remain constant throughout the
871 release test.
- 872 c. The sampling time (at least hourly) and experimental conditions (such as apparatus,
873 temperature, mixing speed) should be defined. The duration of IVRT should be sufficient to
874 characterise the release profile, ideally at least 70% of the active substance applied is released.
875 At least 6 time points should be obtained in the linear portion of the drug release profile,
876 including the first sample immediately after drug diffusion has reached a steady state.
- 877 d. The amount and method of formulation application should be described, consistent ($\pm 5\%$
878 between samples) and validated to ensure homogeneous spreading of the formulation over the
879 membrane and pseudo-infinite dose conditions. The effects of formulation evaporation should
880 be minimised.
- 881 e. The analytical methods should be sensitive enough to quantify the amount of drug in the
882 receptor solution at various time points and validated.

883 *4. Method validation*

884 The marketing authorisation application should include documented evidence that the IVRT has been
885 validated and is suitable for the quality control of the drug product. A summary of the development of
886 IVRT should be provided. Testing conditions providing the most suitable discrimination should be
887 chosen.

- 888 a. Satisfactory evidence of discrimination should be provided, with respect to both of the following
889 quality modifications:
- 890 i. The release rate as a function of drug concentration (at least three strengths) in the
891 formulation should be investigated. The linearity ($r^2 > 0.90$) of the correlation of formulation
892 concentration to rate of drug release (R) should be confirmed when the drug is fully dissolved.
893 For suspensions, the relation between drug concentration and rate of drug release (R) should
894 also be understood and discussed.
- 895 ii. Discriminative power of the proposed method should be demonstrated with altered product
896 formulations with changes in critical quality attributes (such as the active substance particle
897 size distribution or drug product rheological profile), critical manufacturing variables or
898 quantitative excipient composition; the complete omission of one or more specific excipients
899 from the altered product formulation is not supported.
- 900 b. Method intermediate precision for the same batch should be studied with different operators on
901 different days (CV < 10%).

902 c. Method robustness with respect to variations in mixing rate, amount of formulation applied,
903 receptor mediums and temperature should be studied.

904 5. *Presentation of data*

905 A minimum of 12 samples per batch should be used for initial method validation or to demonstrate
906 equivalence. For routine release, a minimum of 6 samples would be accepted.

907 The *in vitro* drug release profile data should be provided in tabular and graphical formats.

908 For the drug release profiles, the quantity of active substance released in mass units per unit area at a
909 given time should be reported.

910 For extended pharmaceutical equivalence testing:

- 911 • The cumulative amount of active substance released versus the square root of time should be
912 linear.
- 913 • The parameter R should be significantly different from zero.
- 914 • The 90% confidence interval for the ratio of means of the test and comparator products for the
915 parameters (R), (A) should be contained within the acceptance interval of 90 – 111%.
- 916 • Lag times should be the same (i.e. within $\pm 10\%$), if present.

918 Annex II In vitro skin permeation studies (IVPT)

919 1. Scope and rationale for IVPT

920 Establishing the characteristic permeation profile of the drug product, using a discriminative *in vitro*
921 permeation test (IVPT), is of value in change control during life-cycle management and an acceptable
922 permeation kinetic test to demonstrate equivalence.

923 For equivalence studies, test and comparator products, together with a negative control such as a
924 formulation with 50% of the proposed product strength, are compared.

925 2. Study design

926 To minimise risk of bias, the study protocol should specify methods of blinding and randomisation in
927 line with ICH E8.

928 A pilot IVPT study comparing the test and comparator products is recommended to confirm that the
929 active substance permeates through the skin, to validate the experimental conditions (such as
930 apparatus, dosing amount, sampling times, stirring rate, etc.) and may be of value in estimating
931 sample size required for the pivotal study.

932 The experimental conditions should be justified with respect to the following:

933 a. Choice of skin membrane:

934 i. It is recommended to use *ex vivo* adult human skin. The study protocol should specify the
935 inclusion/exclusion criteria for skin sections, the anatomical region, condition and duration of
936 skin storage. Skin with tattoos, any signs of dermatological abnormality or exhibiting a
937 significant density of terminal hair should be excluded.

938 ii. Different skin preparation techniques can be used. Evidence should be provided to demonstrate
939 that the skin preparation technique and storage does not introduce artefacts, nor alter the skin
940 barrier function. The use of full-thickness skin may artificially delay drug permeation and
941 should be avoided unless otherwise justified. The skin thickness and separation technique
942 should be described.

943 iii. The skin integrity should be checked prior to and after each experiment. The choice of the skin
944 integrity test and its acceptance criteria should be explained. Different acceptance criteria
945 maybe proposed for before and after the experiment, these acceptance criteria should be
946 justified and consistent across all parallel experiments.

947 iv. Skin from different donors should be chosen.

948 Test, comparator and negative control formulations should be tested using the same donor
949 skin, ideally from adjacent sites, per replicate.

950 v. The number of skin donors should not be less than 12, with at least 2 replicates per donor.

951 vi. The apparatus should ensure consistent temperature control throughout the duration of the
952 experiment. The skin surface temperature should be stable at $32 \pm 1^\circ\text{C}$.

953 b. Choice of receptor medium:

954 i. Sink conditions should be confirmed as described with IVRT (Annex 1).

- 955 ii. The receptor medium should be aqueous buffer, unless otherwise justified. Evidence should be
956 provided that the chosen receptor medium does not compromise the skin barrier integrity
957 throughout the test.
- 958 iii. The inclusion of an anti-microbial agent in the receptor medium, to mitigate potential bacterial
959 decomposition of the skin membrane, is acceptable, but it should not interfere with the
960 properties of the skin or the assay.
- 961 c. The number of sampling time points should be sufficient to obtain meaningful profiles, i.e.
962 capturing the maximal rate of absorption and a decline in the rate of absorption thereafter,
963 with more frequent sampling during the period of greatest change. The duration for testing
964 should be 24 hours. If the study duration is longer than 24 hours, it should be shown that skin
965 barrier function and integrity is adequately maintained.
- 966 d. The recommended dosing amount should be in the range of 2-15mg/cm², based on SmPC
967 posology, unless otherwise justified. Dose application should be validated to ensure
968 reproducibility ($\pm 5\%$) and homogeneous spreading of the formulation over the skin membrane.
969 The donor compartment should be un-occluded unless otherwise specified in the SmPC.
- 970 e. To identify potential contamination and/or interferences, pre-dose samples collected from each
971 diffusion cell and a parallel non-dosed blank control skin experiment are recommended.
- 972 f. A detailed description of the blinding procedure should be provided in the study protocol and
973 final report. The packaging of the test, comparator and negative control products should be
974 similar in appearance to maintain adequate blinding. The method of randomization should be
975 described in the protocol and the randomization schedule provided.
- 976 g. For low strength drug product, the analytical methods should be sensitive enough to quantify
977 the amount of drug in the receptor solution at various time points and be appropriately
978 validated.
- 979 h. The stability of the active substance in the receptor solution over the duration of IVPT study,
980 and sample storage prior to analysis, should be confirmed.

981 *3. Method validation*

982 The Marketing Authorisation Application should include documented evidence that the IVPT has been
983 validated and are suitable for drug product comparison.

984 The suitability of the test conditions should be demonstrated using batches with different quality
985 attributes (a negative control), such as a drug formulation with 50% of the proposed product strength,
986 that is shown to be statistically different and non-equivalent to the comparator product.

987 To achieve this, batches with meaningful changes compared to the applied finished product should be
988 manufactured. Such changes may relate to the quantitative formulation, critical quality attributes
989 and/or using slightly modified process parameters. Current knowledge of the characteristics derived
990 from the active substance and the finished product formulation must be considered when choosing the
991 quality attributes to change. The complete omission of one or more specific excipients from the
992 formulation (e.g., penetration enhancer, preservatives) is not supported.

993 *4. Presentation of data*

994 IVPT data should be provided in tabular and graphical formats. All individual data and parameters
995 should be listed by formulation together with summary statistics. Both the plots of the cumulative
996 amounts permeated per unit area (mass unit/cm²) as function of time and the plot of the rate of
997 absorption (mass unit/cm²/hr) as a function of time should be provided to characterise the release
998 profile.

999 Relevant permeation parameters, e.g., the maximal rate of absorption (J_{\max}) and total amount
1000 permeated at the end of experiment (A_{total}) should be determined and compared.

1001 In the case of a replicate design, results obtained in the duplicate sites from the same donor should be
1002 averaged (geometric mean) prior to further analysis.

1003 The acceptance criteria for equivalence parameters (J_{\max}) and (A_{total}) are:

- 1004 • The 90% confidence interval for the ratio of means of the test and comparator products should
1005 be contained within the acceptance interval of 80.00- 125.00%, unless justified.
- 1006 • Wider 90% confidence interval limits, to a maximum of 69.84 – 143.19, may be accepted in
1007 the case of high variability observed with low strength and limited diffusion drug products, and
1008 if clinically justified. The procedure in the Guideline on Investigation of Bioequivalence,
1009 “Section 4.1.10 Highly variable drugs or drug products” should be followed.

1010 In addition, for the test to be valid:

1011 The acceptance criteria for equivalence parameters (J_{\max}) and (A_{total})

- 1012 • The 90% confidence interval for the ratio of means of the test and *negative control* products
1013 should be entirely outside the interval of 80.00- 125.00%.
- 1014 • The 90% confidence interval for the ratio of means of the comparator and *negative control*
1015 products should be entirely outside the interval of 80.00- 125.00%.

1016 Additional permeation parameters, such as the time of maximal rate of absorption (t_{\max}) and lag-times,
1017 should also be reported. The lag-times between the test and comparator products should be the same
1018 (i.e. within $\pm 10\%$) if present. Any differences in the permeation parameters should be appropriately
1019 discussed with respect to equivalence.

1020 The mass balance should be determined. The cumulative amount of the active substance permeated
1021 into the receptor medium (A_{total}), the total amount of active substance retained (S_{total}) in the skin
1022 samples and amount of active substance retained on the cleaning or experimental equipment (R_{total})
1023 should be presented. The overall recovery of the active substance of 90-110% would be acceptable
1024 without justification, larger variation should be fully justified and explained.

1025 The amount of active substance retained in different skin layers (such as the stratum corneum and
1026 epidermis) may be analysed separately to understand the active substance distribution in human skin.

1028 Annex III Stratum Corneum (S.C.) Sampling (Tape Stripping)

1029 1. Introduction

1030 This annex provides information for an *in vivo* stratum corneum sampling (or tape stripping (TS))
1031 study for semi-solid formulations as a permeation kinetic method to show equivalence, *in lieu* of a
1032 therapeutic equivalence study.

1033 The S.C. sampling study is a minimally invasive technique that involves sequential removal of the
1034 outermost skin layer (i.e., the stratum corneum (S.C.)) using adhesive tapes after application of a
1035 drug-containing formulation. The amount of drug in the S.C. depends on three main processes: drug
1036 partitioning from the formulation into the SC, drug diffusion across the S.C., and drug partitioning out
1037 of the S.C. into the viable tissues. A major advantage of TS is that the experiment is conducted *in vivo*
1038 with a fully functioning cutaneous microcirculation so that drug clearance from the skin is unimpeded.

1039 TS data provide direct measurements and information on the local bioavailability of semi-solid drug
1040 products that act on or in the S.C. e.g. antifungal products. In cases when the target sites of action are
1041 beyond the S.C., TS data may provide a suitable surrogate to characterise the rate and extent of drug
1042 absorption to the underlying tissues.

1043 *In vivo* TS studies are only applicable for products where drug diffusion into and through the SC takes
1044 place. Thus, TS should not be used for testing of drug products to be applied on significantly damaged
1045 skin (e.g. open wounds, burns) or skin of premature new-born. In addition, any products that contain
1046 volatile drugs or target primarily the cutaneous appendages (e.g. hair follicles, sebaceous glands) are
1047 also not suitable.

1048 2. Method development and optimisation

1049 A TS study is not an automated process and careful consideration of the experimental design is vital.
1050 The experimental conditions of the pivotal study should be assessed individually for the concerned
1051 products and should be established by performing a pilot TS study. A summary of the development and
1052 optimisation of the TS method should be provided.

1053 The following experimental conditions should be established and verified during the pilot study:

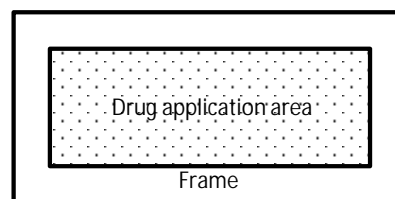
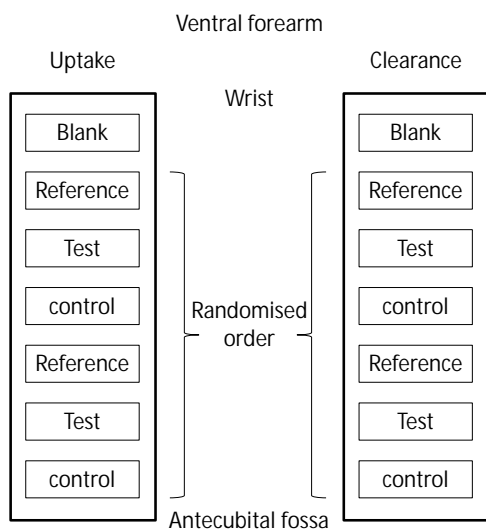
- 1054 • TS study should be conducted on healthy, normal forearm (volar) skin areas with adequate
1055 skin barrier function. The inclusion/exclusion criteria for skin conditions should be defined. Skin
1056 with tattoos, any signs of dermatological abnormality or exhibiting a significant density of
1057 terminal hair should be excluded. The preparation and cleaning procedures prior to the
1058 experiment should be established and further, that the treatment sites are not damaged by
1059 these processes.
- 1060 • Skin integrity should be determined before and after the experiment. This is normally
1061 performed by the measurement of Transepidermal Water Loss (TEWL), although other
1062 techniques may be applicable if appropriate. The acceptance criteria should be fully discussed
1063 and justified.
- 1064 • Due to inter-subject variability, the products to be compared should be applied on the same
1065 subject. Additionally, a negative control that is non-equivalent to the comparator product
1066 should also be included to demonstrate the discriminatory power of the method. It is

- 1067 recommended to blind the investigator responsible for formulation application and tape
1068 stripping to minimise risk of bias.
- 1069 • The dosing amount should be determined based on the SmPC. During the pilot study, the
1070 dosage and area of dose application should be verified to achieve a quantifiable mass of active
1071 substance in the SC. The dosing technique, blinding and randomisation procedures should also
1072 be established.
 - 1073 • A single dose approach should be followed, i.e. skin stripping is performed after a single
1074 application of the test and comparator products.
 - 1075 • It is necessary that the products are compared at two time points (one uptake, one clearance)
1076 for each subject. The optimal uptake and clearance times depend on the characteristics of the
1077 drugs and products and should be determined during the pilot study. Ideally and when relevant,
1078 the uptake time should be sufficiently long for the drug to have attained the diffusional steady-
1079 state. This can be established by testing at multiple uptake times and from which time the
1080 mass of drug recovered from the SC remains constant. The clearance time should be long
1081 enough to allow measurable transfer of drug from the SC into the viable skin (and beyond) but
1082 should not exceed 48 hours to avoid any skin desquamation effect. The clearance time
1083 providing at least a 25% decrease in the mass of drug recovered from the SC with respect to
1084 that at the uptake phase is preferred. In all cases, the sampling times should be carefully
1085 considered and justified.
 - 1086 • The drug product should be removed from the skin surface after the specified uptake time. The
1087 cleaning procedure should be established to ensure that the residual formulation is efficiently
1088 removed from the treatment sites before stripping.
 - 1089 • The adhesive tape chosen should meet the following requirements: a) does not lose mass
1090 when applied and rubbed against the skin surface; b) minimal weight loss and gain during
1091 storage; c) the drug is readily extracted from the SC adhered to the tape; d) the adhesive or
1092 other components of the tape do not interfere with the analytical quantification of the drug;
1093 and e) the adhesive power should be such that the majority of the SC is removed with a
1094 sufficiently low number of tapes (e.g. not more than 30 tapes).
 - 1095 • The TS procedure followed must ensure that most of the SC ($\geq 75\%$) is sampled for each skin
1096 site. The minimum and maximum number of tapes should be established based on the TEWL
1097 (or other relevant) criteria, e.g. eight-fold increment over baseline value, safety stop value.
 - 1098 • Most commonly, the drug is first extracted from the tapes then quantified in the extraction
1099 solvent(s). Alternative methods of extraction/quantification may be used if justified.
1100 Satisfactory efficiency should be demonstrated for the proposed extraction method.

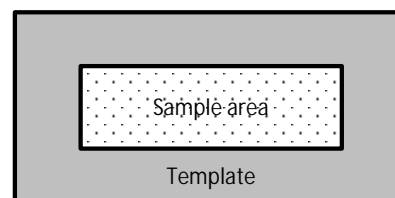
1101 3. Study design

1102 Detailed standard operating procedures should be prepared for the conduct of TS studies to ensure
1103 precise control of dosing, cleaning, stripping, extraction, quantification and other study variables or
1104 potential sources of experimental bias. The inclusion/exclusion criteria should be pre-defined and
1105 clearly stated in the protocol.

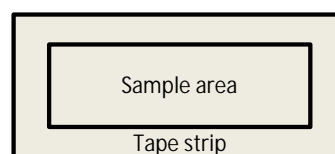
1106 The following study design is recommended for TS studies. The final protocol developed for each
1107 specific case should be justified.



1) Drug is applied to the demarcated area and removed after the specified uptake time.



2) At the end of the uptake phase or after the specified clearance time, a template delineating the sample area is centered on the site.



3) Stripping begins using tapes that are larger than the sample area.

- 1108 • Subjects – TS studies should be performed in healthy volunteers. The subjects should be
- 1109 screened for suitability in line with the principles of bioequivalence studies.
- 1110 • Treatment area –healthy skin of the volar forearm areas sufficient to accommodate at least six
- 1111 application sites per forearm. Skin integrity should be verified e.g. by TEWL measurement. The
- 1112 same number of application sites should be assigned to each forearm;
- 1113 • Number of subjects – the choice of the number of subjects should be justified based on the
- 1114 variability estimated from the pilot studies and demonstrated to be statistically relevant. A
- 1115 minimum of 12 subjects should be used to demonstrate equivalence;
- 1116 • Number of replicates – at least two application sites per product (test, comparator and a
- 1117 negative control) per forearm. One forearm should be used for uptake samples and the other
- 1118 for clearance;
- 1119 • The products should be applied at pre-determined doses ($\pm 5\%$) and spread evenly over the
- 1120 entire demarcated application sites. Blank samples should be collected from the adjacent
- 1121 areas to verify the absence of background levels of drug or other compounds that may
- 1122 interfere with the quantification of drug in the treated SC;
- 1123 • The application sites should be randomised to avoid bias. The application time should be
- 1124 staggered to allow time for S.C. sampling;
- 1125 • Un-occluded conditions, unless occlusion is recommended in the product information, or
- 1126 otherwise justified e.g. to prevent inadvertent removal of formulation.

- 1127 • The formulation should be removed from all treatment sites (uptake and clearance) at the end
1128 of the uptake phase. The total cleaning time should be minimised to avoid any artefacts due to
1129 further drug diffusion. Skin integrity of the treated area should be checked before stripping;
- 1130 • The 'uptake' sites should be tape-stripped immediately after formulation removal. The
1131 'clearance' sites should be tape-stripped at the pre-defined clearance times;
- 1132 • The exact number of tapes required should be determined based on TEWL measurements of
1133 the stripped area and the stopping criteria established from the pilot study;
- 1134 • The mass of SC removed per tape should be determined using a gravimetric method by
1135 weighing the tapes strips before and after stripping. Alternative methods of quantification of
1136 the SC can be used if suitably described and justified;
- 1137 • All stripped tapes collected from each treatment site should be analysed. The first two tapes
1138 should be analysed separately from the remaining tapes, so their contribution to the total
1139 amount of drug recovered can be evaluated. To enhance analytical detectability, the
1140 subsequent tapes can be combined in groups (e.g. each group containing the required
1141 minimum content of SC) for extraction. The total mass of drug in the SC should be calculated
1142 as the sum extracted from all tape strip samples. The mass balance, including the drug content
1143 removed from the surface by cleaning should be determined for each treatment site. The
1144 overall recovery of 90-110% would be acceptable without justification; larger variation should
1145 be fully explained.

1146 *4. Method validation*

1147 Cleaning the skin surface at the end of the application period prior to tape-stripping is important and
1148 must be capable of removing excess formulation (i.e. unabsorbed drug) efficiently without
1149 inadvertently 'driving' the drug into the barrier. The cleaning procedure usually involves quickly and
1150 gently wiping the skin with dry/wet tissue, cotton swabs and/or fresh alcohol wipes. The cleaning
1151 components should be known not to influence drug diffusion into and through the SC. A careful
1152 evaluation and validation of an efficient skin cleaning procedure should be performed prior to the
1153 pivotal study, e.g. by demonstrating satisfactory recovery (>90%) of the drug formulation removed
1154 from the skin surface and the negligible drug content (<10%) recovered by stripping the cleaned skin
1155 immediately after application. Other ways of validation may be used if suitably justified.

1156 The bioanalytical method employed for drug quantification in the tape strips should be validated. The
1157 efficiency of the extraction procedures (including extraction of tape strips in groups) should be
1158 established and demonstrated as consistent prior to the pivotal study.

1159 The discriminatory power of the TS method should be demonstrated for batches with different quality
1160 attributes (a negative control), such as a drug formulation with $\pm 50\%$ of the proposed product
1161 strength, that is shown to be statistically different and non-equivalent to the test and comparator
1162 products. The analytical methods for determining the content of active substance in the tape-stripped
1163 SC should be validated according to the Guideline on Bioanalytical Method Validation.

1164 *5. Data analysis and metrics*

1165 Data from all subjects should be reported and the validity and variability of the results should be
1166 discussed. All treated subjects and application sites should be included in the statistical analysis. The

1167 permitted reasons for exclusion must be pre-specified in the protocol. Data exclusion based on
1168 statistical analysis or for kinetic reasons alone is not acceptable.

1169 For each product, the thickness of SC removed, the number of tapes used and final TEWL value
1170 measured at both uptake and clearance times should be reported. Any differences in these parameters
1171 between the test and comparator products should be discussed with respect to equivalence.

1172 A plot of drug content profile in the SC should be presented for each application site, e.g. the drug
1173 content of each SC tape strip (single or grouped) versus SC depth.

1174 The duplicated measurements for each product in each subject should be averaged (population
1175 geometric mean) prior to analysis.

1176 For the comparison of products, the equivalence parameters: mass of drug recovered from the uptake
1177 (M_{uptake}) and clearance ($M_{\text{clearance}}$) sites, should be statistically compared, according to the Guideline on
1178 the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr).

1179 The acceptance criteria for equivalence parameters (M_{uptake}) and ($M_{\text{clearance}}$) are:

- 1180 • The 90% confidence interval for the ratio of means of the test and comparator products should
1181 be contained within the acceptance interval of 80.00- 125.00%, unless justified.
- 1182 • Wider 90% confidence interval limits, to a maximum of 69.84 – 143.19, may be accepted in
1183 the case of high variability observed with low strength and limited diffusion drug products, and
1184 if clinically justified. The procedure in the Guideline on Investigation of Bioequivalence,
1185 “Section 4.1.10 Highly variable drugs or drug products” should be followed.

1186 In addition, for the test to be valid:

1187 The acceptance criteria for equivalence parameters (M_{uptake}) and ($M_{\text{clearance}}$)

- 1188 • The 90% confidence interval for the ratio of means of the test and *negative control* products
1189 should be entirely outside the interval of 80.00- 125.00%.
- 1190 • The 90% confidence interval for the ratio of means of the comparator and *negative control*
1191 products should be entirely outside the interval of 80.00- 125.00%.
- 1192 • The 90% confidence interval for the ratio of means of the *test product* clearance ($M_{\text{clearance}}$) and
1193 (M_{uptake}) comparator products should be entirely below 1.0.
- 1194 • The 90% confidence interval for the ratio of means of the comparator *product* clearance
1195 ($M_{\text{clearance}}$) and (M_{uptake}) comparator products should be entirely below 1.0.

1196 The overall conclusions of the study should be provided. This should be supported by a sound scientific
1197 discussion and interpretation of the TS data.

1199 Annex IV Vasoconstriction assay for corticosteroids

1200 A description of the protocol for the assay should be provided.

1201 The following testing principles should be followed:

1202 An *in vivo* pilot dose duration-response study should be undertaken to determine the study
1203 requirements for determining the equivalence parameters to be used in the pivotal equivalence study.

1204 Relevant human volunteer inclusion and exclusion criteria should be stated and adhered to for both
1205 pilot and pivotal studies.

1206 Healthy subject with an adequate vasoconstriction to topical corticosteroids must be included.

1207 Test product, vehicle, comparator product, and untreated control should be randomly assigned to
1208 application sites on the ventral forearms.

1209 The study should be appropriately blinded.

1210 For the pivotal study, a minimum of 12 subjects should be included.

1211 The vasoconstriction reaction should be determined at baseline (before drug application), time of drug
1212 product removal, and several times after drug product removal (e.g. 2, 4, 6, 19, 24 hours).

1213 The time course of response should be followed until return to baseline to ensure that maximal
1214 pharmacodynamic response is observed. The assay must be optimised to ensure that the products are
1215 compared in the linear portion of the blanching curve. Several application times should be tested in
1216 pre-test. The lower limit of sensitivity should be determined.

1217 The vasoconstriction reaction should be determined at several time points and AUC data should be
1218 generated. A single time point for estimation of the vasoconstriction reaction is not acceptable.

1219 The measurement of the vasoconstriction reaction should be performed by using a chromameter, or
1220 other methods more sensitive than visual estimation, and by a secondary clinical assessment by an
1221 independent observer.

1222 References:

1223 1 FDA Guidance for Industry: Topical Dermatologic Corticosteroids: *in vivo* bioequivalence 2 June
1224 1995.

1225 2 "Quantification of corticosteroid-induced skin vasoconstriction", *Dermatology*, (2002), 205, 3-
1226 10.

1227 3 "The skin-blanching assay", *Journal of the European Academy of Dermatology and Venerology*
1228 (2012), 26, 1197-1202.