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4

5 **Guideline on the quality requirements for drug-device**
6 **combinations**
7 **Draft**

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42 **Executive summary**

43 This guideline provides guidance on the documentation expected for Drug-Device Combinations (DDCs)
44 in the quality part of the dossier for a marketing authorisation application or a variation application.

45 For the purpose of this guideline, medicinal products which contain one or more medical device(s) as
46 an integral part of the composition, as well as medicinal products for which one or more medical
47 device(s) and/or device component(s) are necessary for use of the medicinal product are defined as
48 DDCs. The types of DDCs within the scope of this guideline are medical device(s) and/or device
49 component(s) that are integral to the medicinal product or non-integral (i.e. co-packaged with the
50 medicinal product or referenced in the medicinal product information and obtained separately).

51 **1. Introduction (background)**

52 In recent years there has been an increase in the number of scientific advice requests and marketing
53 authorisation applications (MAAs) where a medicinal product incorporates, either in an integral or non-
54 integral manner, a medical device/medical device component (hereafter, both terms are called
55 “device(s)”, for definitions see Section 10) for the use of the medicine.

56 The availability of commercialised devices with automated functions is increasing and this may benefit
57 patients with regular and long-term dosing requirements in an outpatient setting, either by self-
58 administration or with the support of a professional or lay caregiver. This reduces the burden on
59 patients and on healthcare systems.

60 In this guideline, the terms ‘integral’ and ‘non-integral’ are used to describe DDCs as follows:

61 Integral DDCs are products falling under the second sub-paragraphs of both Article 1(8) and Article 1(9)
62 of the Regulation (EU) 2017/745 on medical devices (the MDR). These Articles describe the two types
63 of integral drug-device combination products authorised under the medicines’ framework:

- 64 1. Devices that when placed on the market or put into service incorporate, as an integral part, a
65 substance that, if used separately, would be considered as a medicinal product, provided that the
66 action of the substance is principal (Article 1(8) MDR).
- 67 2. Devices intended to administer a medicinal product, where they form a single integral product
68 intended exclusively for use in the given combination and which is not reusable (Article 1(9) MDR).
69 Typically, these devices have measuring, metering or delivery functions.

70 Examples of medical devices in integral DDCs are:

- 71 ▪ Devices for delivery to site of action e.g. the dropper on the top of the container with eye drops or
72 the mouthpiece on the top of spray cans for throat sprays.
- 73 ▪ Single dose pre-filled syringes, pens and injectors.
- 74 ▪ Multi-dose pens and injectors containing a pre-filled cartridge where the cartridge cannot be
75 replaced, and the pen is not designed for subsequent use with a new cartridge.
- 76 ▪ Drug-releasing intra-uterine devices; pre-assembled, non-reusable applicators for vaginal tablets.
- 77 ▪ Dry powder inhalers that are assembled with the medicinal component and ready for use with single
78 or multiple doses but cannot be refilled when all doses are taken.

- 79 ▪ Implants containing medicinal products whose primary purpose is to release the medicinal product.
80 ▪ Medicinal products with an embedded sensor.

81 Non-integral DDCs are those DDCs for which the two or more separate components (i.e. medicinal
82 product(s) and device(s)) are not physically integrated during manufacturing but where the medicinal
83 product and the specific device(s) are combined for administration.

84 Devices in non-integral DDCs are those that are co-packaged and supplied along with the medicinal
85 product, or where the Product Information (SmPC and Package Leaflet) refers to a specific device to be
86 used with the medicinal product but the device is obtained separately. In either case, devices not
87 falling within the scope of Article 1(8) and 1(9) of the MDR should be CE marked. Non-integral medical
88 devices that are co-packaged and those that are obtained separately are discussed in separate sections
89 of Chapter 6.

90 Examples of medical devices in non-integral DDCs are:

- 91 ▪ Oral administration devices (e.g. cups, spoons, syringes)
92 ▪ Injection needles and filter needles
93 ▪ Refillable pens and injectors (e.g. using cartridges)
94 ▪ Reusable dry powder inhalers; spacers for inhalation sprays
95 ▪ Nebulisers, vaporisers
96 ▪ Pumps for medicinal product delivery
97 ▪ Electronic tablet dispensers

98 **2. Scope**

99 DDCs falling within the definition of Article 1(9) of the MDR are the primary focus of this guideline;
100 however, it is recognised that DDCs as defined by Article 1(8) of the MDR will likely become more
101 common-place as technology develops. DDCs falling within the definition of Article 1(8) of the MDR are
102 within the scope of this guideline and should follow the basic principles defined herein, recognising that
103 certain elements of this guideline may not be applicable. It is also recognised that not all aspects of
104 this guideline may be applicable depending on the type of DDC. In such cases, it is recommended to
105 consult with a competent authority for the regulation of medicines or seek scientific advice. This
106 guideline is not exhaustive, and applicants should also consider all other relevant guidelines related to
107 quality aspects of medicinal products.

108 This guideline covers specific quality dossier requirements to be provided for in an MAA and
109 subsequently during the product lifecycle for integral and non-integral DDCs, as defined in the
110 introduction. It applies to DDCs where the medicinal product constituent is either a chemical, biological
111 or radiopharmaceutical.

112 With respect to ATMPs, this guideline applies only to devices that are considered part of the container
113 closure system, or medical devices that are co-packaged or referenced in the Product Information and
114 obtained separately. Article 117 of the MDR does not apply to ATMPs.

115 The following are out of scope of this guideline:

- 116 a) Combined ATMPs (where devices are part of the active substance and/or the formulation). The
117 ATMP Regulation 1394/2007 applies for MAAs for combined ATMPs.
-

- 118 b) Electromechanical components of devices (including active implantable devices) and electronic add-
119 ons to existing products.
- 120 c) Veterinary DDCs.
- 121 d) *In-vitro* diagnostic devices.
- 122 e) Medical devices incorporating, as an integral part, a medicinal substance or human blood derivative
123 with a mode of action ancillary to that of the device.

124 **3. Legal basis**

125 This guideline should be read in conjunction with:

- 126 ▪ Directive 2001/83/EC (the Medicinal Products Directive, MPD) and Regulation 726/2004/EC (as
127 amended), and
- 128 ▪ Regulation (EU) 2017/745 on medical devices (the Medical Devices Regulation, MDR) which amends
129 Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009, and which
130 repeals Directive 93/42/EEC (the Medical Device Directive, MDD).

131 In addition, this guideline should be read in conjunction with all other relevant directives and
132 regulations, the European Pharmacopeia and all relevant Commission, ICH and CHMP guidelines, Q&A
133 documents and other documents as linked to or published on the EMA website.

134 **4. General considerations**

135 As a general principle for the DDCs considered in this guideline, the assessment of the suitability of a
136 device for its intended purpose should take into account both the relevant quality aspects of the device
137 itself and its use with the particular medicinal product. The complexity of the device, relevant patient
138 characteristics and the clinical setting in which the DDC is to be used are also important aspects of the
139 review process. The medicinal product dossier should include full evaluation of the impact of the device
140 on the Quality Target Product Profile (QTPP), Critical Quality Attributes (CQA) and overall control
141 strategy of the medicinal product.

142 In accordance with Article 117 of the MDR, an MAA for an integral DDC shall include evidence of the
143 conformity of the device part with the relevant General Safety and Performance Requirements (GSPRs)
144 as follows:

- 145 1. Where available, an EU Declaration of Conformity issued by the device manufacturer, or a
146 Certificate of Conformity issued by a Notified Body (NB) that allows a CE mark to be displayed on
147 the device.
- 148 2. If the above information (on results of the conformity assessment) is not available:
 - 149 (a) for medical devices that, if used separately, do not require the involvement of a NB, the
150 applicant's confirmation that the device part meets the relevant GSPRs, or
 - 151 (b) if the conformity assessment of the device, if used separately, would require the involvement
152 of a NB, a Notified Body opinion (NBOp) on the conformity of the device with the relevant
153 GSPRs, issued by an appropriately-designated NB.

154 Refer to Section 5.4 (3.2.R) below for further details.

155 The **core precept** of this guideline is that the Competent Authority for the regulation of medicines
156 (CA) will evaluate the device specific aspects of safety and performance relevant to the quality, safety
157 and efficacy of the medicinal product, and that, as applicable, the NB will assess the relevant GSPRs.

158 Non-integral DDCs should be CE marked in accordance with the MDR. Where a CE marked device for
159 the administration of the medicinal product is co-packaged or is referred to in the SmPC of a marketing
160 authorisation, additional information may need to be provided by the applicant with regards to the
161 device if the device may have an impact on the quality, safety and/or efficacy of the medicinal product.

162 In cases of doubt as to the proposed classification of the device according to the MDR, it is
163 recommended that an opinion be sought from a medical device CA.

164 The requirements laid down in the guideline relate to the quality of the DDC, including the
165 manufacturing and control methods thereof. It is not intended to address the obligations of the
166 manufacturers of the medical device(s). It is however, acknowledged that specific information may be
167 required to fulfil the requirements of other EU guidance (e.g. ICH guideline M7).

168 Samples of the DDC should be provided on request.

169 **4.1. Application of Standards**

170 Compliance of a DDC with relevant Ph. Eur. chapter(s) or monograph(s) should be demonstrated.
171 Ph.Eur. requirements and European and ICH guidance take precedence over ISO standards.

172 **4.2. Submission of data, its location in the dossier and its format**

173 Information on the device should be provided in a clearly structured manner, following the electronic
174 Common Technical Document (eCTD) format (Volume 2B Notice to Applicants Medicinal Products for
175 Human Use – Presentation and Format of the Dossier). In sections 5 and 6 below, guidance is provided
176 on information to be included in specific sections of Modules 1-3. Cross-reference may be made
177 between sections in order to avoid repetition.

178 With regards to the structure of Module 3, Section 3.2.P should contain information on the product-
179 specific quality aspects related to the device relevant to the quality, safety and efficacy of the
180 medicinal product. Section 3.2.R should include relevant information related to the demonstration of
181 compliance of the device(s) with MDR Annex 1 (the GSPRs) e.g. NBoP, NB Certificate of Conformity
182 and/or device manufacturer's EU Declaration of Conformity.

183 In general, Module 3 of the MAA dossier should include appropriate information on the manufacture,
184 control and usability of the DDC as defined for the intended patient population. Usability and human
185 factor studies are multidisciplinary in nature and could be included in section 5.3.5.4, 'Other Clinical
186 Study Reports' of the CTD, with appropriate reference to Module 3 as these may be reviewed by both
187 pharmaceutical and clinical assessors, each with different focus.

188 For ATMPs, the content of the MAA may be adapted, provided that this is justified under a risk-based
189 approach.

190 **4.3. Platform technology/technologies**

191 Discussion and justification for the use of platform technology/technologies (for definition, see Section
192 10) should be included. A summary of the (relevant) data for those aspects of the device which pertain

193 to the 'platform' should be presented; these should be clearly indicated in relevant sections of Module
194 3.2.P and should include references to detailed information presented in 3.2.R. Suitability with regards
195 to specific products and subsets of the target patient population should be demonstrated. Reference to
196 previously approved DDC(s) developed and marketed by the marketing authorisation holder (MAH)
197 may be included as supportive information, as well as other relevant quality aspects in support of the
198 proposed approach.

199 **4.4. Scientific advice**

200 This guidance covers the main aspects of the quality requirements for DDCs to be submitted as part of
201 an MAA. However, it is not possible to cover all types of devices and/or future technological
202 developments that may raise novel questions and/or require complex scientific assessment.
203 Consideration should be given to seeking advice within the EU Competent Authority (medicines)
204 network early in development, particularly for new and/or emerging technologies (see Section 9).

205 **5. Integral DDCs**

206 **5.1. Module 1, Product Information**

207 SmPC Section 1: The name of the medicinal product should include the device presentation in line with
208 EDQM standard terminology for pharmaceutical form.

209 SmPC Section 4.2: The directions for proper use of the DDC should be described (including cleaning of
210 the device as necessary), in line with relevant guidance. A device tradename may be stated.

211 SmPC Section 6.3: Information on DDC in-use shelf-life should be included, if relevant.

212 SmPC Section 6.4: DDC storage conditions should be listed.

213 SmPC Section 6.5: The type of the device(s) and its (their) component material(s) should be listed.

214 SmPC Section 6.6: Product-specific information should be provided for preparation or handling
215 (including disposal of the device(s)).

216 Package Leaflet: Information should be consistent with the SmPC, provide clear and simple instructions
217 on the intended use of the DDC for patients and/or for healthcare professionals (HCP) and be written in
218 such a way as to prevent medication errors. Information related to the use of the DDC, consistent with
219 the device Instructions For Use (IFU), if applicable, should be included.

220 Package leaflet and labels: The outer packaging and the Package Leaflet may only include symbols or
221 pictograms if necessary, to clarify certain information compatible with the SmPC (e.g. instructions for
222 use) which may be useful for the patient, to the exclusion of any element of a promotional nature.

223 For a device that has a CE mark, the CE mark may be included on the device itself but should not be
224 included on the labelling for the DDC as this may be interpreted incorrectly as referring to the DDC as
225 a whole.

226 **5.2. Module 3.2.P, Drug Product**

227 **P.1 Description and Composition**

228 Concise information on integral DDCs, and if applicable, any additional devices provided and used with
229 the medicinal product, should be submitted. The description and function of each device should be
230 stated.

231 **P.2 Pharmaceutical Development**

232 This section of the dossier should summarise all information relevant to development of the device as
233 integrated into the medicinal product, including the rationale for its selection. The suitability of the
234 device for its intended use, in the context of the device performing as intended and protecting the
235 medicinal product etc., should be demonstrated. A clear narrative of device and medicinal product
236 development including all relevant data (e.g. justification of any new device, pharmaceutical form,
237 etc.) should be provided. The suitability of the DDC and its materials of construction to protect the
238 drug product formulation from light, moisture, microbial contamination and vapour phase permeation
239 (as appropriate) should be confirmed. Any interactions of the device with the medicinal product should
240 be discussed and justified, as appropriate.

241 It is recommended that a risk assessment summary for the DDC, aligned with suitable risk assessment
242 principles in ICH Q9 and/or DIN EN ISO 14971, is presented.

243 **P.2.1 Components of the Drug Product**

244 A high-level description of the DDC should be provided, cross-referring to other sections as
245 appropriate.

246 **P.2.2 Drug Product**

247 The applicant must take into consideration the intended use of the device and its suitability within the
248 context of the DDC, its therapeutic indication and the relevant target patient population.

249 Where required (e.g. due to changes in device design during development), summary bridging data
250 (see Section 7) should be provided in this section of the dossier, with cross-references to relevant data
251 in Module 4 or Module 5, as appropriate. Appropriate data should be provided to demonstrate and
252 justify the equivalence of the overall performance of the DDC prototype(s) used during pivotal clinical
253 development with the DDC intended for marketing.

254 **P.2.3 Manufacturing Process Development**

255 A concise description of the DDC manufacturing process development should be described in line with
256 relevant guidance. The development, justification and suitability of sterilisation processes of any
257 devices or the DDC should be described, where relevant.

258 A comparison of the manufacturing process of DDCs from pivotal or bridging clinical studies to the
259 commercial DDC should be presented.

260 The development of the control strategy for the DDC manufacturing process should be described.

261 **P.2.4 Container Closure System (CCS)**

262 The following aspects of the development of the container closure system should be considered:

263 Description and rationale for DDC

264 A brief description of the container closure system should be presented, including the rationale for the
265 container and device component(s) and its (their) materials of construction, including, for example:

- 266
- 267 ▪ Any non-integral medical devices needed for correct use of the DDC.
 - 268 ▪ Confirmatory signals for dose delivery (e.g. audible click), sharps injury prevention features, safety/lock-out features to prevent over-dosage, safe disposal information, etc.
 - 269 ▪ For implantable/transdermal devices, information on the matrix and reservoir, including mechanism
270 of drug release.
 - 271 ▪ Brief details of critical functional components e.g. power supply, dose-setting mechanism,
272 description of controls and alarms and their instructions for use etc.
 - 273 ▪ Brief description and rationale for any related technologies e.g. a software application.
 - 274 ▪ If the device includes a graduation marking, the requirements of Quality of Medicines, Questions
275 and Answers on the EMA website should be considered.

276 Functional Performance

277 Functional performance aspects of the DDC should include dose accuracy and precision, mechanical
278 functionality and/or other functionalities directly related to the intended use of the device with the
279 medicinal product and its impact on quality, safety and/or efficacy.

280 The ability of the device to deliver the medicinal product in an accurate and reproducible way should be
281 demonstrated as per the posology stated in Section 4.2 of the SmPC. The following should be
282 considered:

- 283
- 284 ▪ Test conditions should, as far as possible, simulate the use of the DDC (e.g. dose delivery
285 performance from an eye drop bottle should be evaluated from the dropper in various orientations)
under relevant (in-use) storage conditions.
 - 286 ▪ Consistency of dose delivery should be demonstrated throughout the (in-use) shelf-life of the DDC
287 (e.g. beginning, middle and end). The precision and accuracy of dosing should be guaranteed from
288 release until the end of shelf life and also during the use of the particular DDC under the conditions
289 recommended in the SmPC (in-use stability testing).
 - 290 ▪ Issues related to usage e.g. shaking, priming, dropping test.

291 For usability (human factor) studies, see 3.2.R (Section 5.4, below).

292 Compatibility

293 Compatibility between device and drug product should be investigated to provide appropriate and
294 supportive information. The following aspects should be considered:

- 295
- 296 ▪ The physical and chemical compatibility of the drug product with the device(s) should be
297 demonstrated. All materials in contact with the drug product should be considered. Interaction
studies, including extractable and leachable studies as appropriate, should be performed. These
-

298 should include physical and chemical compatibility (e.g. sorption, precipitation of drug substance in
299 solution, and stability, etc.).

300 ▪ If processing aids (e.g. lubricants, glue/adhesive from labels etc.) are used with the device and
301 come into direct contact with the drug product, leachable studies should be performed to evaluate
302 their effects on the drug product as well as on the performance of the device(s). For example,
303 silicone oils released from the device components can nucleate the formation of proteinaceous
304 particles/aggregates with protein products. Toxicological assessments of processing aids that are in
305 direct contact with the drug product should be performed, as necessary.

306 ▪ Compatibility should be considered from a chemical and physical stability perspective i.e. under
307 different orientations, in-use conditions and during simulated transportation studies.

308 ▪ The suitability of the device for the particular drug product (e.g. considering the rheological
309 properties of the drug product) should be discussed and justified.

310 ***P.2.5 Microbiological Attributes***

311 For sterile products, the integrity of the DDC throughout use and shelf-life, as it relates to preventing
312 microbial contamination should be demonstrated.

313 ***P.3 Manufacture***

314 ***P.3.1 Manufacturers***

315 Manufacturer names/addresses for DDC assembly, packaging, DDC sterilisation, labelling and quality
316 control sites, as well as for the EU batch release site(s) should be stated.

317 ***P.3.3 Description of manufacturing process and process controls***

318 The description of the manufacturing process of the DDC should include operations relating to the
319 combination of device(s) and drug product. Critical processes, technologies and/or packaging
320 operations that directly affect product quality should be described in detail.

321 The following information should be included:

322 ▪ Description of any operations that are performed on the device(s) by the DDC manufacturer (such
323 as subassembly steps, washing, coating, sterilisation, or depyrogenation etc.). Information on the
324 sites performing these steps could be presented in this section of the dossier or reference given to
325 section P.7.

326 ▪ Description of the DDC manufacturer(s)' sterilisation methods and conditions for the device(s),
327 where relevant. The sterilisation method(s) used should be validated.

328 ▪ A description of the filling steps and the final assembly of the device(s) into the DDC, as performed
329 by the DDC manufacturer should be detailed together with critical process parameters, in-process
330 controls and acceptance criteria (for critical steps).

331 ▪ For applied labels which include printed markings, the position of the label on the container should
332 be specified and acceptable tolerances for the label positioning defined as critical in-process controls
333 (IPCs) in Module 3.2.P.3.3 and Module 3.2.P.3.4.

334 **P.3.4 Controls of critical steps and intermediates**

335 Any critical steps should be justified, and any device-specific intermediates should be defined, along
336 with relevant specifications, test methods and their validation. Any holding times should be defined and
337 justified.

338 **P.3.5 Process validation and/or evaluation**

339 Process validation for the manufacture of the DDC should be performed in line with relevant European
340 guidelines, including the assembly and sterilisation of the device(s) (if applicable) and any filling steps.

341 **P.5 Control of drug product**

342 **P.5.1 Specification(s)**

343 When appropriate, the specification should include the following:

- 344 ▪ Description of DDC appearance.
- 345 ▪ Performance tests relevant to the intended use of the DDC e.g. extractable volume, delivered dose
346 uniformity and functionality of the device at both release and shelf life.
- 347 ▪ Other critical test parameters related to CQAs of the medicinal product, e.g. glide force, needle
348 penetration force, seal integrity, delivery time, exposed needle length after activation of device
349 (needle penetration depth, relevant to route of administration), activation force, transdermal
350 adhesion properties, lock-out system control to prevent over-dosing and signals to confirm dose
351 delivery to the patient/user.

352 **P.7 Container closure system**

353 Where the device is part of the container closure system as intended for marketing, the following
354 information should be provided:

- 355 ▪ A description of the container closure system, including the materials of construction of each
356 primary packaging and device component and its specification.
- 357 ▪ Information on sites and processes for sterilisation and/or subassembly of device(s), or reference to
358 section P.3. When empty, sterile, ready-to-use container closure components are purchased,
359 information should be provided in line with the EMA Sterilisation guideline
360 (EMA/CHMP/CVMP/QWP/BWP/850374/2015). Where a sterile CE-marked device is used, the
361 inclusion of the NB Certificate of Conformity is sufficient to demonstrate sterility.
- 362 ▪ Suitable quality control specifications of medical device(s) and/or device components.
- 363 ▪ Detailed specifications and test procedures (including description, identification and functional tests
364 as relevant), as well as critical dimensions, technical drawings and photographs of primary and
365 functional secondary packaging materials. The secondary packaging should be designed with
366 consideration to the use and mechanical resistance of the DDC.
- 367 ▪ Evidence of compliance with the relevant Ph. Eur. monographs, if applicable, and/or food contact
368 Directives, as appropriate (such as declarations of compliance from suppliers).

369 **P.8 Stability**

370 Stability studies for the DDC should include the following tests/studies:

- 371 ▪ Functionality tests (e.g. dose delivery per actuation, syringeability, communication with software,
372 etc.). In case of complex DDCs, such as integral ingestible devices, additional functional tests
373 related to the intended use of the medicinal product are required.
- 374 ▪ In-use stability testing performed under the conditions of use as stated in the SmPC, unless
375 otherwise justified.
- 376 ▪ Microbial quality, sterility, content/potency and purity for the entire shelf-life and in-use period, as
377 appropriate.
- 378 ▪ Simulated transport studies that encompass chemical (e.g. degradation) and physical (e.g.
379 vibration) stability, where relevant.

380 **5.3. Module 3.2.A.2, Adventitious Safety Evaluation**

381 All materials of human or animal origin used in the manufacturing process of the DDC, or such
382 materials coming into contact with the device during its manufacturing process, should be identified.
383 Information assessing the risk with respect to potential contamination with adventitious agents of
384 human or animal origin should be provided in this section.

385 TSE agents

386 Where appropriate, a TSE statement confirming compliance of the component(s) of the DDC with
387 EMEA/410/01 rev.3, to the European Standard “Medical devices utilising animal tissues and their
388 derivatives – part 3 (EN ISO 22442-3:2007)” and Ph. Eur. 5.2.8 “Minimising the risk of transmitting
389 animal spongiform encephalopathy agents via human and veterinary medicinal products” should be
390 provided in this section.

391 Viral safety

392 Where applicable, an assessment of the risk to the DDC with respect to potential viral contamination
393 should be provided in this section. The viral risk assessment should be made in accordance with the
394 European Standard “Medical devices utilizing animal tissues and their derivatives – part 3 (EN ISO
395 22442-1:2015)” and Ph. Eur. 5.1.7 Viral safety.

396 For substances from human blood/plasma, compliance with relevant EU directives (the Blood directive
397 2002/98/EC and its associated technical directives), Ph. Eur. and EMA guidelines should be verified.

398 Other adventitious agents

399 Detailed information regarding other adventitious agents, such as bacteria, mycoplasma and fungi
400 should be provided in relevant sections pertaining to the device within the core dossier, as appropriate.

401 **5.4. Module 3.2.R, Regional Information, Medical Device**

402 An index should be provided, which should cross refer to studies or information provided in 3.2.P and
403 Module 5 sections as appropriate.

404 Section 3.2.R should include information related to demonstration of compliance of the device(s) with
405 MDR Annex 1 (i.e. the applicable GSPRs) as follows:

406 1. Where available, an EU Declaration of Conformity issued by the device manufacturer, or a
407 Certificate of Conformity issued by a NB that allows a CE mark to be displayed on the device.

408 2. If the above information on results of the conformity assessment is not available:

409 (a) If the device is a class I device (excluding Im, Is, Irsi): the applicant's confirmation that the
410 device part meets the relevant GSPRs, or

411 (b) If the device is a class Im, Is, Irsi, IIa, IIb or III: an NBOp on the conformity of the device
412 with the relevant GSPRs, issued by an appropriately-designated NB.

413 3. For medical devices that are used as container closure system for ATMPs, the applicant should
414 provide evidence that the relevant GSPRs are met, as follows:

415 (a) EU Declaration of Conformity issued by the device manufacturer, or

416 (b) Certificate of Conformity issued by a NB, or

417 (c) Confirmed by the applicant (e.g. by providing summary information in form of checklist).

418 Section 3.2.R may also include, if relevant, cross-reference to studies or additional information
419 provided in 3.2.P sections.

420 Notified Body Opinion

421 Article 117 of the Medical Device Regulation (MDR) (EU) 2017/745 has introduced amendments to
422 Annex I section 3.2 (12) of Directive 2001/83/EC concerning the documents that need to be submitted
423 to CAs assessing MAAs for medicinal products incorporating a device as an integral part. These
424 products are covered by the second subparagraph of Article 1(8) and the second subparagraph of
425 Article 1(9) of the MDR.

426 Article 117 states (sic)..."*If the dossier does not include the results of the conformity assessment [...] and where for the conformity assessment of the device, if used separately, the involvement of a notified body is required [...], the authority shall require the applicant to provide an opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation issued by a notified body.*"

431 The amended provisions of point 12 of Section 3.2 of Annex I to Directive 2001/83/EC, require
432 applicants for MAAs of medicinal products incorporating as an integral part a device, to submit the
433 results of the assessment of the conformity of the device part with the relevant GSPRs set out in Annex
434 I to the MDR. If the application dossier does not contain these results and where the conformity
435 assessment of the device, if used separately, requires the involvement of a NB, the applicant is
436 required to provide an opinion on the conformity of the device with the relevant general safety and
437 performance requirements set out in Annex I to the MDR issued by a NB. It should be ensured that the
438 NB is appropriately accredited for the issuance of such an opinion.

439 The processes by which a NB derives their opinion are not within the scope of this guideline; however,
440 to facilitate review of the DDC, to enable both the assessor and applicant to determine how the NB
441 opinion was formed, avoid duplication of assessment and identify aspects to be considered during the
442 MAA, it is recommended that the NBOp is presented as a technical summary report. Annexes 1 and 2

443 provide guidance on the type of data to be included in the NBOp and propose a template to harmonise
444 its format.

445 Usability (human factor) Studies

446 If the device has not been used in the proposed patient population before or if the setting of use is new
447 and different from the intended use as confirmed by the certificate of conformity or NBOp (e.g. a
448 prefilled syringe used for the first time in an outpatient setting or used for the first time in patients
449 with conditions which could impair use), a usability study – to evaluate whether the DDC can be used
450 safely to deliver the medicinal product to the target population - is expected. In this case, detailed
451 information on usability and human factors studies (or justification for their absence) should be
452 presented in Module 5, and a summary should be provided in Module 3.2.R (cross-referencing the
453 detailed study in Module 5). In all other circumstances, a study summary should be presented in 3.2.R.
454 This is considered a multidisciplinary topic and will also be reviewed outside of quality considerations.

455 Where evidence of usability is required, this may be supported by published and/or other relevant data
456 for identical/similar devices on the market. However, if usability cannot be satisfactorily demonstrated
457 in this way, a formal usability study is required to demonstrate usability of the medicinal product by
458 the intended population. Applicants are encouraged to follow/use relevant harmonised standards to
459 demonstrate compliance such as IEC 62366-1:2015 and IEC/TR 62366-2:2016.

460 Platform technology/technologies

461 Detailed information pertaining to the discussion presented in Section 4.3, should be presented in this
462 section.

463 **6. Non-Integral DDCs**

464 The characteristics of non-integral devices used for the administration of medicinal products may
465 impact the quality, safety and efficacy profile of the medicinal products. To the extent that
466 administration devices are co-packaged with the medicinal product or, in exceptional cases, where the
467 use of a specific type of administration device is specifically provided for in the Product Information of
468 the medicinal product, additional information may need to be provided in the MAA on the
469 characteristics of the medical device(s) that may impact on the quality, safety and/or efficacy of the
470 medicinal product.

471 Requirements regarding quality aspects for non-integral DDCs are presented below. Given the broad
472 range of non-integral devices, the information to be provided in this section will depend on the
473 specifics of the device and the risks thereof to the quality, safety, and/or efficacy of the medicinal
474 product. There are separate guideline sections for devices that are co-packaged and for those that are
475 obtained separately and referred to in the product information.

476 ***6.1. Non-Integral DDCs with co-packed medical devices***

477 ***6.1.1. Module 1, Product Information***

478 Unless otherwise justified, where specific device(s) is (are) necessary for the correct use of a medicinal
479 product and is (are) co-packaged with the medicinal product, the specific device(s) should be defined
480 in the product information.

481 SmPC Section 4.2: The directions for proper use of the DDC should be described (including cleaning of
482 the device as necessary), in line with relevant guidance. A device tradename may be stated.

483 SmPC Section 6.3: Information on the in-use shelf-life of the DDC should be provided, if relevant.

484 SmPC Section 6.4: DDC storage conditions should be listed.

485 SmPC Section 6.5: The type of the device(s) and its (their) component material(s) should be listed.

486 SmPC Section 6.6: Product-specific information should be provided for preparation or handling
487 (including disposal of the device(s)).

488 Package Leaflet: Information should be consistent with the SmPC, provide clear and simple instructions
489 on the intended use of the DDC for patients and/or for HCPs and be written in such a way as to
490 prevent medication errors. Information related to the use of the device, consistent with the device IFU,
491 if applicable, should be included.

492 Package Leaflet and labels: The outer packaging and the Package Leaflet may only include symbols or
493 pictograms if necessary to clarify certain information compatible with the SmPC (e.g. instructions for
494 use) which may be useful for the patient, to the exclusion of any element of a promotional nature.

495 **6.1.2. Module 3.2.P, Drug Product**

496 **P.1 Description and Composition**

497 A brief description and function of any device(s) used to administer the DDC should be stated.

498 **P.2 Pharmaceutical Development**

499 It is expected that the use of a medicinal product with a specified device is demonstrated to be safe
500 and effective. This section should summarise relevant Quality information for the device including
501 safety and performance, in the context of the device reproducibly delivering the required dose of the
502 medicinal product within the intended use. This section should provide evidence for the suitability of
503 the device(s) in its (their) intended use, provide a clear narrative of device and medicinal product
504 development, and provide all relevant data (including justification of any new device, pharmaceutical
505 form or excipient, etc., not previously used, where relevant). The amount of information provided in
506 this section should reflect the risk of the device to impact the quality, safety and/or efficacy of the
507 medicinal product.

508 A brief description of the device, and of the functionality of the device, together with the medicinal
509 product, should be provided. It is not expected to be as detailed as the information provided in 3.2.R
510 for the device (i.e. cross-referencing with relevant sections of 3.2.R is expected).

511 **P.2.1 Components of the Drug Product**

512 A high-level description of the devices(s)/DDC should be provided.

513 **P.2.2 Drug Product**

514 A general discussion on the choice of device should be provided, including the intended use (usability),
515 rationale for choice of device, etc.

516 The functional aspects of the device should be qualified in line with its complexity and should include
517 the rationale for the choice and optimisation of the design and performance (such as dose-delivery
518 performance and mechanical functionality of the device). Dose accuracy/delivered dose uniformity
519 should be demonstrated with the intended medicinal product. Any markings/graduation should be
520 justified in line with the posology stated in Section 4.2 of the SmPC. Details of the cleaning of the
521 device(s) should be stated, where relevant.

522 ***P.2.5 Microbiological Attributes***

523 For medicinal products intended to be used sterile, the sterility of the non-integral device should be
524 verified (e.g. by reference to the CE certificate). Maintenance of sterility throughout use and shelf-life
525 of the final medicinal product should also be demonstrated.

526 ***P.2.6 Compatibility***

527 Unless otherwise justified, compatibility between device and drug product throughout use and shelf-life
528 of the DDC should be investigated:

- 529 ▪ Compatibility should be considered from an in-use stability perspective and the physical and
530 chemical compatibility of the drug product with the device(s) should be demonstrated (e.g.
531 sorption, precipitation of drug substance in solution, stability, etc.). Interaction studies should be
532 performed, as appropriate, using a risk-based approach. All materials in contact with the drug
533 product should be considered.
- 534 ▪ The suitability of the device for the particular drug product (e.g. considering the rheological
535 properties of the product) should be discussed and justified.

536 ***P.7 Container Closure System***

537 Although in the non-integral DDC setting, the device is not part of the container closure system, a brief
538 description of the device should be provided in this section (for example; "1 mL glass syringe including
539 0.05 mL marked graduations", along with the name and/or identification number of the device). The
540 specification applied to the incoming device upon receipt by the drug product manufacturer should be
541 presented. For further details, reference should be made to the information in 3.2.R, including
542 evidence of the CE mark.

543 ***P.8 Stability***

544 If relevant, in-use stability data should be provided for the drug product in contact with the device,
545 including device functionality that may impact the quality, safety and/or efficacy of the medicinal
546 product.

547 ***6.1.3. Module 3.2.A.2, Adventitious Safety Evaluation***

548 If self-declared, the requirements for 3.2.A.2 as for the integral DDCs should be followed. Otherwise, a
549 valid NB Certificate of Conformity can be accepted as evidence of compliance with EU requirements.

550 **6.1.4. Module 3.2.R, Regional Information, Medical Device**

551 An index should be provided, which should cross refer to studies or information provided in 3.2.P
552 sections as appropriate.

553 An EU Declaration of Conformity issued by the device manufacturer should be provided as evidence of
554 the CE-mark. For devices of risk classes above Class I (i.e. Im, Is, Irsi, IIa, IIb and III) an NB
555 Certificate of Conformity should also be provided.

556 Where applicable, and depending on the complexity of the device, any changes implemented in the
557 design of the device during the development of the medicinal product should be discussed in terms of
558 the impact on product performance characteristics (e.g. delivered dose, needle penetration force for
559 subcutaneous/intramuscular injection and other usability factors). Appropriate data should be provided
560 to demonstrate and justify the similarity of the overall performance during clinical phases with that
561 after approval.

562 Where required and applicable (e.g. owing to changes in device design), summary bridging data should
563 be provided in this section of the dossier, with cross-reference to relevant data in Module 4 or Module
564 5, as appropriate (see Section 7).

565 If the device has not been used in the proposed patient population before or if the setting of use is
566 new, a usability study - that the device/medicinal product can be used safely to deliver the required
567 dose to the target population – is expected. Where evidence of usability is required, this may be
568 supported by published or other relevant data for identical/similar devices on the market. However, if
569 usability cannot be satisfactorily demonstrated in this way, a formal usability study is required (see
570 also Section 5.4).

571 Detailed information on usability and human factors studies (or justification for their absence) should
572 be presented in Module 5. A summary should be provided in Module 3.2.R, cross-referring to Module 5.

573 Discussion of, and justification for the use of platform devices should be included in this section (for
574 further detail, see Section 4.3 above).

575 **6.2. Non-Integral DDCs with separately obtained devices**

576 This section explains the data requirements that should be provided as part of MAA for medicinal
577 products in the following scenarios:

- 578
- 579 ▪ ATMPs, where devices used during surgical procedures for application, implantation or
administration of the product, may have an impact on its efficacy or safety.
 - 580 ▪ In exceptional cases where the use of a specific medical device is provided for in the SmPC of the
581 marketing authorisation because of the impact thereof on the quality, safety and/or efficacy profile
582 of the medicinal product.

583 The impact of the specific device on the medicinal product (when used together) should be addressed
584 using a risk-based approach, with consideration as to the need for a usability study. This should be
585 documented in 3.2.P.2. If a separately obtained device referred to in the product information is used,
586 then there must be evidence of efficacy and safety/bioequivalence for the medicinal product in
587 combination with the device.

588 The product information should be sufficiently detailed to ensure correct use of the medicinal product
589 with the specific device. Refer to Section 6.1.1 above.

590 In section 3.2.P.2, it is expected that data on compatibility, dosing accuracy, handling, manipulation
591 etc. are presented as appropriate.

592 In section 3.2.P.8, it is expected that in-use stability data are presented, if applicable.

593 Information on usability and human factors studies should be presented, unless otherwise justified
594 (see Section 5.4 above).

595 **7. Bridging to devices used in clinical development**

596 Given the (often) critical contribution that a device makes to the safe and effective administration of a
597 drug product, it is expected that the device be as advanced as possible in the development process
598 (i.e. meets the relevant GSPRs) by the time pivotal clinical trials start.

599 While authorisation of clinical trials is a national issue and outside the remit of this guideline, in the
600 context of the MAA, the following guidance is provided:

601 ▪ Integral DDC: there is no requirement for evidence of compliance with the relevant GSPR to be
602 provided for devices within integral DDCs used in clinical development. It is expected that the
603 impact of any changes in devices during the pivotal clinical trials be described, evaluated and
604 justified in terms of any potential impact of the changes on the quality, safety and efficacy of the
605 medicinal product, from the beginning of the pivotal trials to the product that is proposed for
606 market in the MAA. Where changes are made to the device, data to bridge the different device
607 designs from a safety and efficacy perspective may be required in Modules 3 and 5. A risk
608 assessment should be included in Module 3.2.P.2.4, which should describe the changes, batches
609 used and trial(s) affected, and what mitigation was performed to minimise the impact on product
610 quality.

611 ▪ Non-integral DDC: where (device) clinical investigations were incorporated into the pivotal DDC
612 clinical trial, because of their relevance to the MAA and because they could not be separated from
613 the investigation of the medicinal product, the rationale for this approach should be discussed and
614 justified in Module 5.

615 **8. Lifecycle Management**

616 A change listed in the variation guideline will require a variation of the appropriate category to be
617 submitted to the medicines CA(s). All changes to medical devices and/or device components within
618 DDCs should be presented in accordance with the relevant EU Variations Regulation and associated
619 variation guidelines in place and should be submitted under the appropriate category.

620 Depending on the nature of the change, the MAH should consider whether updates to relevant
621 documentation (e.g. NBOp, Declaration of Conformity, CE mark etc.) associated with the device in
622 question are required to support the change.

623 The category of variation should take into consideration the impact of the change, e.g. a change to a
624 device that impacts any DDC CQAs and/or any element(s) of the overall DDC control strategy may be
625 considered a higher category of variation. In cases where the need for a variation is unclear and/or the

626 category of the change is unclear, it is recommended that the medicines CA that issued the MA is
627 consulted to agree the category prior to submission of the variation application.

628 ***Additional considerations***

629 In cases where a variation is submitted to change or replace the device of a DDC, consideration should
630 be given to whether there is an impact on the instructions for use between current and proposed
631 devices, and any potential risks of user or medication error. The overall risk assessment of the DDC
632 should be updated accordingly. Consideration should be given to the following:

- 633 ▪ Communication plans may be needed in order to make patients and/or HCPs aware of the change.
- 634 ▪ Timing for when the applicant plans to make the updated DDC available should be clear and
635 justification for how long the currently registered DDC will remain on the market should be given, if
636 required.
- 637 ▪ If the instructions for use are different between current and proposed devices, the potential risks of
638 user error and the potential for medication errors, should be considered. The risks may be due to
639 familiarity with previous device instructions, complexity of new/revised device(s), etc. Human
640 Factors/usability studies may be required.
- 641 ▪ If there is a risk of a medication error because of the introduction of a new/revised device(s), this
642 may need to be captured in the Risk Management Plan (RMP).

643 **9. Emerging Technologies**

644 It is recognised that developments in science and technology for medical devices may advance more
645 rapidly than for medicinal products alone. This guideline provides basic requirements to be expected in
646 a quality dossier for an MA; it is recognised that alternative approaches for emerging technologies
647 could be followed, if adequately justified.

648 If the DDC will be utilising emerging technologies, it is recommended to engage with medicines CAs in
649 a timely manner, e.g. by formal scientific advice, or through Innovation Offices, etc. It is also
650 recommended to identify and engage in discussions with a NB in a timely manner.

651 The provision of a sample or samples of the DDC to the assessors in order to simulate use is strongly
652 encouraged to aid assessment and minimise queries relating to hands-on, practical aspects of its use.

653 **10. Definitions**

654 **Applicant**

655 The commercial entity responsible for the marketing authorisation application of the DDC in the EU.

656 **Control Strategy (as per ICH Q10)**

657 A planned set of controls derived from current product and process understanding that ensures process
658 performance and product quality. The controls can include parameters and attributes related to drug
659 substance and drug product materials and components, facility and equipment operating conditions,
660 in-process controls, finished product specifications, and the associated methods and frequency of
661 monitoring and control.

662 **Container Closure System (CCS)**

663 The sum of components that together contain and/or protect the medicinal product, including devices,
664 as defined in Section 1 of this guideline.

665 **Dossier**

666 The complete body of data submitted for regulatory review. In this case, the dossier relates to the
667 administrative and quality components of the (e)CTD, i.e. Module 1 (administrative), Module 2 (Overall
668 Summaries) and Module 3 (quality) respectively, and typically specifically in relation to the content of
669 Module 3.

670 **Drug-Device Combination Product (DDC)**

671 A medicinal product(s) with integral and/or non-integral medical device/device component(s)
672 necessary for administration, correct dosing or use of the medicinal product. For specific examples of
673 the definition as interpreted for this guideline, see Section 1, above.

674 **Drug Product Manufacturer**

675 The commercial entity legally responsible for manufacture of the integral or non-integral (co-packaged)
676 DDC.

677 **Device Manufacturer**

678 The commercial entity manufacturing and supplying sterile/non-sterile devices and/or components to
679 the drug product manufacturer for incorporation into the DDC.

680 **Marketing Authorisation Holder (MAH)**

681 The company that has been granted a marketing authorisation for a medicinal product (e.g. a DDC) by
682 the competent authorities of (a) member state(s) in accordance with Directive 2001/83/EC (as
683 amended) or Regulation (EC) No 726/2004 and is responsible for marketing the product.

684 **Medical Device (synonyms: Device, MD)**

685 A device that fulfils the definition of Article 2(1) MDR and is intended to be placed on the market, made
686 available on the market or put into service in the EU.

687 **Medical device component**

688 A device that fulfils the definition of Article 2(1) MDR, where it is considered a constituent part of a
689 marketing authorisation (integral or non-integral). It is synonymous with medical device.

690 **Medicinal Product (synonyms: MP, Drug Product, DP)**

691 Refer to Article 1(2) of Directive 2001/83/EC.

692 **Notified Body Opinion (NBOp)**

693 An opinion provided by a Notified Body on the conformity of the device component(s) of an integral
694 DDC with the relevant GSPPs set out in Annex I of Regulation 2017/745, as required by Article 117 of
695 the MDR. Refer to Annexes 1 and 2 of this guideline for a proposal of a NBOp template and associated
696 documentation.

697 **Performance**

698 The action of the medical device in performing its intended function.

699 **Platform technology**

700 A technology that has already been approved for another medicinal product and has therefore been (at
701 least partly) characterised previously.

702 **Usability**

703 Evidence that the DDC can be used safely to deliver the medicinal product to the target population.
704 This is also known as human factors engineering and/or usability engineering.

705 **Abbreviations**

706	(c)ATMP	(combined) Advanced Therapy Medicinal Product
707	CE	Certificate European
708	CA	Competent Authority (for the regulation of medicines, either National or EMA)
709	CCS	Container Closure System
710	CHMP	Committee for Human Medicinal Products
711	CQA	Critical Quality Attribute
712	CS	Control Strategy
713	DDC	Drug-Device Combination product
714	DHPC	Direct Healthcare Professional Communication
715	EMA	European Medicines Agency
716	GSPR	General Safety and Performance Requirement
717	HCP	Healthcare Professional
718	ICH	International Council for Harmonisation of Technical requirements for Pharmaceuticals
719		for Human Use
720	IFU	Instructions for Use (device)
721	ISO	International Organisation for Standardization
722	MA	Marketing Authorisation
723	MAA	Marketing Authorisation Application
724	MAH	Marketing Authorisation Holder
725	MDR	Medical Device Regulation (EC 2017/745)
726	MPD	Medicinal Products Directive (2001/83/EC, as amended)
727	NB	Notified Body
728	NBOp	Notified Body Opinion
729	Ph.Eur.	European Pharmacopoeia
730	PL	Package Leaflet
731	Q&A	Question and Answers
732	SmPC	Summary of Product Characteristics

733 **Annex 1: Proposal for Notified Body Opinion template**

734 NB logo
735 NB name and address
736 NB number

737
738
739
740 **Notified Body Opinion**
741 (Article 117 of the Medical Device Regulation (EU 2017/745))
742
743 Compliance of device(s) incorporated into an integral drug-device combination product
744 with
745 Annex I (General Safety and Performance Requirements)
746 Medical Device Regulation (EU 2017/745)

747
748
749
750
751

752 Administrative reference number: _____
753 (including version number)

754
755

756 Reviewer name and position: _____
757

758 NB authorisation (signature): _____
759

760 Authorisation date (YYYY/MM/DD) _____
761

762

763 **I. SUMMARY OF NOTIFIED BODY OPINION**

764

765 **<Clearly state opinion i.e. acceptable or not acceptable>**

766 **<Include a brief summary highlighting the basis of the opinion, with any relevant**

767 **constraints or other considerations>**

768

769 **II. LIST OF ABBREVIATIONS**

770

771 <Insert list of abbreviations>

772

773 **III. ASSESSMENT OF THE GENERAL SAFETY AND PERFORMANCE REQUIREMENTS**
774 **(GSPR)**

775

776 **a. Basis of assessment, Article 117 of Regulation EU 2017/745.**

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b. General Drug-Device Combination product information.

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791

<Summary information to ensure mutual understanding of the product under assessment including a detailed description of product, in particular the device component(s) indications, method of administration, intended use, etc.>

792

c. Scope of assessment

793

<List of applicable GSPRs, with justification for any omissions>

794

795

d. Assessment

796

<This should form the main body of the report>

797

798

<For each applicable GSPR, summarise the data presented, and final outcome(s) of the assessment>

799

800

801

<Any changes made to the device during pivotal clinical trials should be described (changes, timelines) and the impact on relevant GSPRs discussed>

802

e. Notified Body Opinion

803

804

<Clearly state the opinion and a summary of the justification for the NB opinion>

805

806 **IV. REFERENCES**

807 <List relevant references, including ISO standards>

808 **Annex 2: Template cover sheet for Notified Body Opinion**

809 It is intended that this document is completed in two situations:

- 810 1. Where an application is made for a stand-alone medicinal product. In this case, the MAH
 811 completes this section.
 812 2. Where an application is made that utilises a platform technology. In this case, it is the technology
 813 owner who completes this section, effectively providing a letter of authorisation to the MAH to use
 814 the data, similar to the approach used where a CEP holder authorises the use of the active
 815 substance in an EU procedure.

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GENERAL INFORMATION

PRODUCT DETAILS	
Invented / Trade name of the medicinal product	<as per MAA>
Applicant	<Name and address of MAH i.e. legal entity holding the MA>
Marketing authorisation type	<e.g. Centralised application>
Marketing authorisation procedure number	<e.g.>
Pharmaco-therapeutic group (ATC code)	<e.g. D08A C52>
Indication(s)	<As per SPC4.1>
Pharmaceutical form(s) and strength(s)	<e.g. 10mg, 20mg INN solution for injection, pre-filled syringe>
INN (or common name) of the active substance(s):	<as per MAA>
Authorisation to use NBOp	<Suitably authorised / signed by either the MAH, applicant or the platform technology holder>

820