

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL
REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

**THE COMMON TECHNICAL DOCUMENT FOR
THE REGISTRATION OF PHARMACEUTICALS
FOR HUMAN USE: QUALITY
M4Q(R2)**

Draft version

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M4Q(R2)
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ICH HARMONISED GUIDELINE

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REGISTRATION OF PHARMACEUTICALS FOR
HUMAN USE: QUALITY**

M4Q(R2)

ICH Consensus Guideline

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SCOPE AND ORGANISATION

The M4Q(R2) guideline establishes the location and structure of quality information for registration applications of all medicinal products for human use. It supports various submission types, including those referring to or consisting of master files, and applies to both initial marketing authorisation and post-approval submissions. This guideline is structured to be flexible to accommodate all types of medicinal products and their components.

The applicant should consult applicable ICH and regional guidelines, including those for master files, to determine the appropriate sections and content for their specific product. Any non-applicable sections should be left out. Illustrative examples included in the guideline are meant to further clarify location of potentially relevant content but are not exhaustive and should not be interpreted as requirements.

The M4Q(R2) structure is presented in a globally harmonised format with sufficient granularity to facilitate digitalisation and organised for easy access, analysis, and knowledge management. This granularity also supports inclusion of information from emerging concepts, such as advanced manufacturing, use of structured data management processes, artificial intelligence/machine learning, bioinformatics, and advanced analytical tools. The applicant should include applicable information on these tools within the relevant sections of the dossier pertinent to their specific application. Novel processes or technologies that directly impact product quality may be described in greater detail to ensure clarity and comprehension.

The M4Q(R2) guideline organises information across Module 2.3 and Module 3 in a complementary manner. Module 2.3 serves as the basis for regulatory assessment and facilitates lifecycle management, however it does not supersede regional post approval change requirements. Module 2.3 provides for a sufficiently comprehensive overview and evaluation of the medicinal product and its components applying science- and risk-based principles. Module 2.3 includes sections for general information (2.3.1), overall development and control strategy (2.3.2), core quality information (2.3.3), and development summaries and justifications (2.3.4). Additionally, Module 2.3 may include product lifecycle management information (2.3.5) and product quality benefit-risk considerations (2.3.6). Module 3 serves as a repository for detailed descriptions of methods, data, and other relevant quality information that supports Module 2.3. Information in 2.3.1, 2.3.2, 2.3.4, 2.3.6, and Module 3 is supportive. The applicant may amend or supplement the information for post-approval submissions.

The quality information for materials of the medicinal product is organised within corresponding sections across Module 2.3 and Module 3.2. These sections are aligned with the roles of these components, including Drug Substances (DS), Substance Intermediates (SI), Raw Materials (RM), Starting Materials (SM), Reference Standards/Materials (RS), Excipients (EX), Impurities (IM), Drug Products (DP), Product Intermediates (PI), Packaged Medicinal Products (PM), Pharmaceutical Products (PH), and Medical Devices (MD). These sections are further organised using the following structure: Description, Manufacture, Control, and Storage:

- Description: Identifies the material and its key characteristics;
- Manufacture: Outlines the production process and process controls;
- Control: Describes quality control measures such as specifications;
- Storage: Provides container closure system, stability, storage condition, and retest period/shelf life.

45 This structure ensures consistency and efficiency of information management. Figure 1
46 illustrates the relationships among 2.3.3 Core Quality Information, 2.3.4 Development
47 Summary and Justifications, and Module 3.2 Body of Data in the context of the structure used
48 for materials.

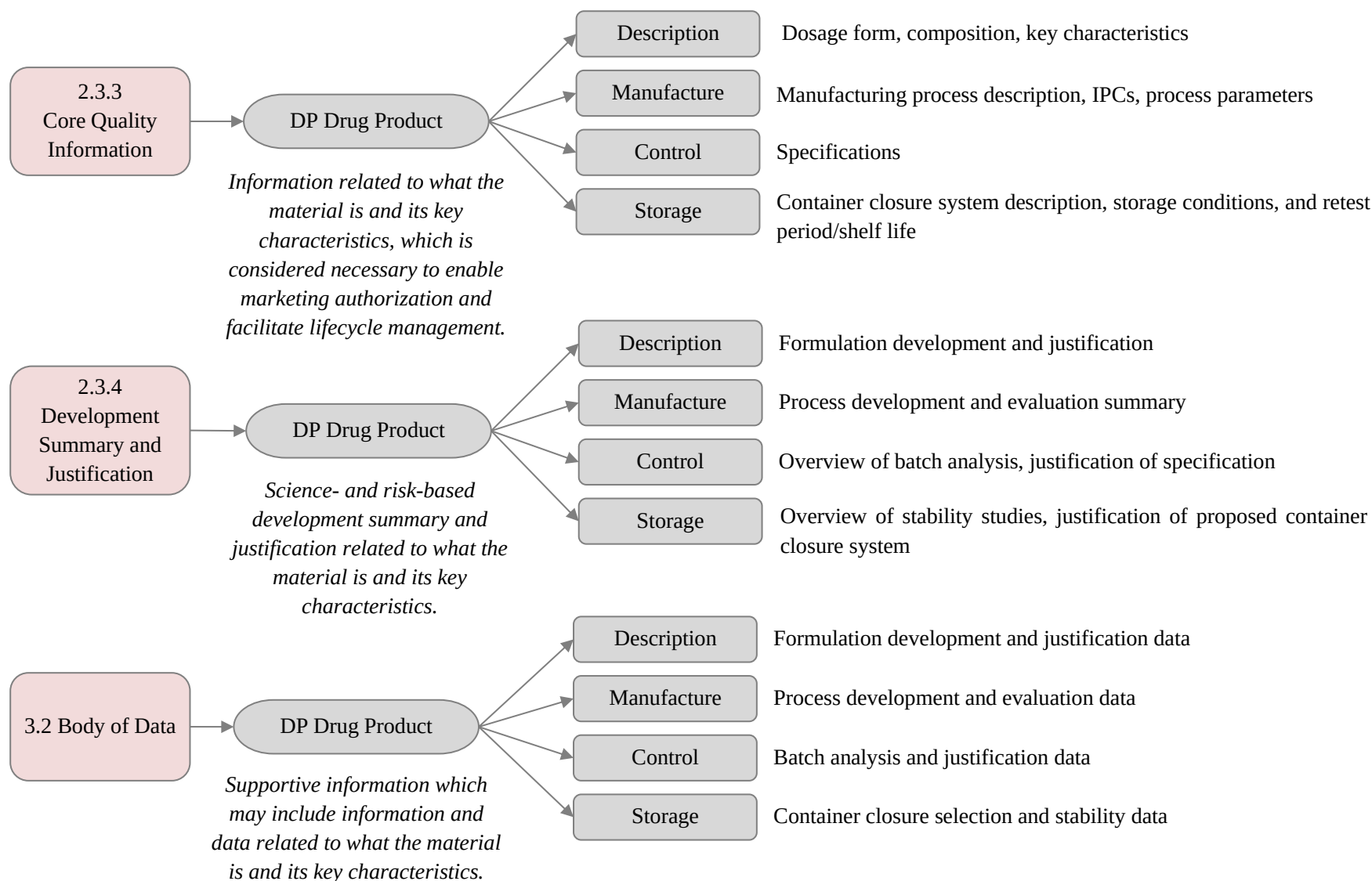
49 Sections not directly tied to material information adopt a different categorisation and header
50 logic. This allows for flexibility in presenting information relating to Analytical Procedures
51 and Facilities, with direct explanations provided within relevant sections.

52 Section headers may include mandatory keywords in parentheses () or optional keywords in
53 square brackets [] to uniquely identify a section's content and distinguish between multiple
54 instances.

55 ICH M4Q(R2) aims to foster harmonisation of the quality dossier content, ideally enabling the
56 submission of a single M4Q(R2) version of the dossier across countries or regions. When a
57 country or regional requirement cannot be avoided due to legal obligations, the applicant may
58 provide additional information specific to the country or region directly in the relevant section.

59 **Figure 1: Illustration of relationships among sections 2.3.3 Core Quality Information, 2.3.4 Development Summary and Justifications, and Module 3.2 Body of Data**
60 **in the context of DMCS Model used for materials.**

61



62

63 **MODULE 2. COMMON TECHNICAL DOCUMENT SUMMARIES**

64 **2.3. Quality Overview**

65 **2.3.1 General Information**

66 The following information should be provided, when applicable:

- 67 • non-proprietary or common name of the drug substance(s);
- 68 • non-proprietary or common name of the drug product(s);
- 69 • dosage form(s) and drug release profile(s);
- 70 • strength(s) and the form of the drug substance for the expression of strength;
- 71 • route(s) and methods of administration;
- 72 • primary packaging;
- 73 • medical device(s) or any co-packaged item(s);
- 74 • maximum daily dose.

75 A schematic representation of the product's configuration (e.g., a picture) may be included to
76 illustrate the product components and their functional relationships.

77 **2.3.2 Overall Development and Overall Control Strategy**

78 This section provides a high-level overview of the medicinal product's development and
79 control strategy, aiming to facilitate understanding and supporting an efficient assessment. The
80 Overall Control Strategy (OCS) is built upon the concepts defined in ICH Q8 considering the
81 patient's needs and reflects the Core Quality Information. This section includes:

- 82 • Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQAs)
83 (2.3.2.1);
- 84 • Overall product development strategy (2.3.2.2); and
- 85 • Representation of how the individual control strategies contribute to the OCS (2.3.2.3).

86 For the submission of restricted part of, or stand-alone master file for material (e.g., drug
87 substance), an overall development strategy and a representation of the overall control strategy
88 should be provided (ICH Q8, Q11).

89 The information in this section may be updated throughout the product lifecycle to reflect any
90 relevant changes in the Core Quality Information (CQI).

91 **2.3.2.1 Quality Target Product Profile**

92 The QTPP should be provided (ICH Q8).

93 **2.3.2.1.1 Critical Quality Attributes**

94 A list of the CQAs should be provided, preferably in a tabulated format, with a brief
95 justification for their selection. When necessary, a cross-reference to other subsections of 2.3.4
96 may be included (ICH Q6A/Q6B, Q8, Q9, and Q11).

97 **2.3.2.2 Overall Development Strategy**

98 This section should provide a concise overview of the development rationale to help

contextualise the development strategy, highlighting the pivotal decisions made along the development to achieve the intended quality.

This overview serves as a high-level introduction to how the CQAs were used to guide drug substance, product, and process development, in line with ICH Q8 and Q11 guidelines. Cross-references may be included to more detailed information in 2.3.4 or Module 3.

Where applicable, the use of an enhanced approach, including the establishment of design space, as well as prior knowledge and platform technologies should be briefly discussed, illustrating how these resources were used for the development process. While not intended as an exhaustive summary, this discussion should provide enough details to understand the reasoning behind key development choices, particularly those that affect multiple aspects of product design.

2.3.2.3 Overall Control Strategy Representation

The OCS is a holistic and integrated approach encompassing considerations from the CQAs to the end-to-end controls, describing how the individual control strategies interact to ensure product quality (ICH Q6A/Q6B, Q8, Q9, Q10, and Q11). A representation, such as a table, diagram, or flowchart of the proposed OCS should be included. This representation may cross-reference other sections of Module 2.3 (e.g., 2.3.3 CQI).

The OCS should address the manufacturing process from the introduction of starting/source materials to the final drug product, including packaging. The OCS may also address the pharmaceutical product after transformation and any device to be used with the drug product, where relevant to ensure product quality or performance.

The OCS should cover the control strategies only for the material(s) (e.g., drug substance) included in the application or submission.

For applications referring to master file(s), the information provided by the master file holder (e.g., the open part of a master file) should be considered. If applicable, relevant information, such as specifications and manufacturing processes, should be incorporated into the OCS.

2.3.3 Core Quality Information

The applicant should describe the information considered necessary to support a science- and risk-based regulatory assessment to enable marketing authorisation and facilitate lifecycle management. This section should include all information subject to lifecycle management per regional post-approval change requirements to ensure product quality.

The applicant should maintain the CQI throughout the product lifecycle to ensure that product quality information remains current. When Established Conditions (ECs) per ICH Q12 are approved, lifecycle management activities should follow the approved Product Lifecycle Management Document (PLCM) in 2.3.5.2. However, the identification of ECs should not result in a reduction of information submitted in the marketing authorisation application.

2.3.3.DS Drug Substances

(Drug Substance Name) [Manufacturer]

The information for each drug substance or manufacturing site should be organised following the guidelines specified in this section. The applicant may repeat this section as needed. If the information for each manufacturing site is the same, there is no need to repeat the sections.

140 **2.3.3.DS.D Description**
141 *(Drug Substance Name) [Manufacturer]*

142 **2.3.3.DS.D.1 Nomenclature**

143 This section should include information on the nomenclature of the drug substance, such as
144 recommended international non-proprietary name (INN), regional non-proprietary name (e.g.,
145 USAN, BAN, JAN), WHO Reference Number, company code, Chemical Abstracts Service
146 (CAS) registry number, compendial name, and other chemical names.

147 **2.3.3.DS.D.2 Structural characteristics**

148 This section should include the structural characteristics of the drug substance, based on the
149 nature of the substance.

150 For chemical entities, this section should include, for example, the structural formula, including
151 relative and absolute stereochemistry, the molecular formula, confirmation of structure based
152 on synthetic route, spectral analysis, and the relative molecular mass.

153 For biologics, this section should include, for example, relevant structural characteristics,
154 including a description of the molecular structure, the schematic amino acid sequence
155 indicating glycosylation sites or other posttranslational modifications, and relative molecular
156 mass. The degree and profile of structural heterogeneity of the biologically active variants
157 should also be illustrated.

158 **2.3.3.DS.D.3 General properties**

159 This section should include a summary of general properties of the drug substance and their
160 impact on the CQAs of the drug product.

161 For chemical entities, these properties may include, for example, selected crystalline form, pH,
162 ionic strength, particle size distribution, hygroscopicity, and solubility.

163 For biologics, a description of biological activities and immunological properties should be
164 included, where relevant.

165 **2.3.3.DS.M Manufacture**
166 *(Drug Substance Name) [Manufacturer]*

167 **2.3.3.DS.M.1 Description of the manufacturing process**

168 This section should include sufficient information on the drug substance commercial
169 manufacturing process along with a flow diagram/process schematic, which represents the
170 sequence of unit operations and the scale of production, including substance intermediate(s), if
171 applicable. The diagram should indicate points of sampling at which in-process controls (IPCs),
172 intermediate tests, or final drug substance controls are conducted. If applicable, the applicant
173 should identify the unit operations conducted in batch mode or in a continuous manufacturing
174 process, any process models utilised, and describe the proposed design space, if any (ICH Q8,
175 Q13).

176 Batch size/scale, starting/source materials, aseptic processing procedures, and intermediates
177 should be defined.

178 For chemical entities, this section should include chemical structures in the diagram/schematic

179 and quantities of raw materials.

180 For biologics, this section should include intermediates and their holding times, and major
181 equipment.

182 For sterile drug substances, a description of the method of sterilisation along with appropriate
183 acceptance criteria should be included.

184 For continuous manufacturing, aspects that are not typically associated with batch processes
185 should be provided, including equipment design and dimensions (ICH Q11, Q13).

186 Any reprocessing steps should be identified and included in the process flow diagram (ICH
187 Q7).

188 *2.3.3.DS.M.2 Process controls*

189 This section should include process parameters and in-process controls that are essential for
190 ensuring that a drug substance of the required quality will be produced consistently. The
191 information should include associated test methods (with cross-references to the relevant
192 analytical procedures 2.3.3.AP) and control ranges/acceptance criteria, organised per unit
193 operation.

194 When models are associated with the process parameters and IPCs, a description/identification
195 of the models used should be included in 2.3.3.AP.

196 **2.3.3.DS.C Control**

197 *(Drug Substance Name) [Manufacturer]*

198 This section should include the specification(s) for the drug substance, including tests, name
199 of the analytical procedures, and acceptance criteria for release and/or retest period/shelf life
200 with applicable standards/pharmacopeia(s). Cross-references to relevant Analytical Procedures
201 sections should be provided, including any proposed real time release testing (RTRT) approach
202 (ICH Q6A/Q6B, Q11, Q14, M7).

203 When models are associated with the analytical procedures for release and/or stability testing
204 of the drug substance, this section should include a description/identification of the models
205 used in 2.3.3.AP.

206 **2.3.3.DS.S Storage**

207 *(Drug Substance Name) [Manufacturer]*

208 *2.3.3.DS.S.1 Container closure system*

209 This section should include information about the container closure system proposed for the
210 bulk material (biologics) and drug substances. Specifications for primary packaging material
211 and for functional secondary packaging materials that are critical to drug substance quality
212 should be included (ICH Q11).

213 *2.3.3.DS.S.2 Stability, storage conditions, and retest period/shelf life*

214 This section should include information about the proposed retest period/shelf life and storage
215 conditions. The post-approval stability protocol and stability commitment should be included
216 (ICH Q1/Q5C).

217 For biological bulk material and drug substance, storage conditions, shelf life, and shipping
218 conditions should be specified. If applicable, the traceability (chain of custody and chain of
219 identity) should be included.

220 **2.3.3.SI Substance Intermediates, if Applicable**

221 *(Substance Intermediate Name) [Manufacturer] [Drug Substance Name]*

222 This section should include information for substance intermediates with established
223 specifications. For intermediates controlled through in-process controls, the applicant should
224 provide this information in 2.3.3.DS.

225 For most chemical entities, only 2.3.3.SI.C will be populated.

226 For biologics (e.g., the antibody used for an antibody drug conjugate or viral vectors used for
227 *ex vivo* gene modified Advanced Therapy Medicinal Products (ATMPs)), information should
228 be provided for Description, Control, and Storage, as applicable. The applicant may provide
229 the Manufacture information separately or integrated into 2.3.3.DS.M.

230 This section may be used to describe the manufacture of specific substance intermediates
231 separately from the main drug substance manufacturing process. This may be relevant for
232 highly complex end-to-end biological drug substance manufacturing processes or cases where
233 the sub-part of the end-to-end drug substance manufacturing process, up to a specific substance
234 intermediate, is performed by a different manufacturer.

235 **2.3.3.SI.D Description**

236 *(Substance Intermediate Name) [Manufacturer] [Drug Substance Name]*

237 If applicable, this section should include information on the description of the substance
238 intermediate to the same level of detail as under each corresponding heading in 2.3.3.DS.D.

239 **2.3.3.SI.M Manufacture**

240 *(Substance Intermediate Name) [Manufacturer] [Drug Substance Name]*

241 For a substance intermediate manufactured by the same manufacturer and as part of the drug
242 substance manufacturing process, an integrated manufacturing process description should be
243 presented under 2.3.3.DS.M. This information should be provided separately in this section
244 only if deemed necessary and the content should align with 2.3.3.DS.M.

245 **2.3.3.SI.C Control**

246 *(Substance Intermediate Name) [Manufacturer] [Drug Substance Name]*

247 This section should include specification(s) for the substance intermediate(s) and references to
248 relevant analytical procedures. If applicable, a description of any proposed RTRT approach
249 should be included (ICH Q6A/Q6B, Q11, Q14).

250 **2.3.3.SI.S Storage**

251 *(Substance Intermediate Name) [Manufacturer] [Drug Substance Name]*

252 If applicable, this section should include information on the container closure system, stability,
253 storage conditions, retest period/shelf life, and shipping conditions to the same level of detail
254 as under each corresponding heading in 2.3.3.DS.S.

255 **2.3.3.SM Starting/Source Materials**

256 *[Starting Material Name] [Drug Substance Name] [Intermediate Substance Name]*

257 This section should include information in accordance with guidelines specified (ICH Q5A,
258 Q5B, Q5D, Q11).

259 **2.3.3.SM.D Description**

260 *[Starting Material Name] [Drug Substance Name] [Intermediate Substance Name]*

261 This section should include a description of the starting/source material which allows for
262 unambiguous identification (e.g., chemical structure, molecular weight), as appropriate. If the
263 starting/source material is biologically sourced (e.g., a cell bank, or cells used in manufacture
264 of allogeneic or autologous ATMPs), information on its source should be provided.

265 **2.3.3.SM.M Manufacture**

266 *[Starting Material Name] [Drug Substance Name] [Intermediate Substance Name]*

267 Where appropriate, this section should include information on the manufacturer/supplier of the
268 starting materials.

269 For biological starting materials, information on the procedures used to generate new Working
270 Cell Banks (WCB)/seed lots, and/or cell modification procedures should be provided, if
271 applicable. Generation of Master Cell Banks (MCB) should be described in 2.3.4.SM (ICH
272 Q5B, Q5D).

273 Information about how animal/human-derived materials are obtained (e.g., procurement
274 information, manufacturing process) should be included.

275 **2.3.3.SM.C Control**

276 *[Starting Material Name] [Drug Substance Name] [Intermediate Substance Name]*

277 This section should include specifications for starting/source materials with a cross-reference
278 to 2.3.3.AP, as appropriate. Testing information should be provided for cell banks/seed lots.
279 For animal or human-derived starting materials, information about control of adventitious
280 agents of the starting/source materials, including donor eligibility screening and testing for
281 ATMPs, should be provided, as appropriate (ICH Q5A). If applicable, the applicant should
282 discuss control of adventitious agents in 2.3.4.IN.2.2.

283 **2.3.3.SM.S Storage**

284 *[Starting Material Name] [Drug Substance Name] [Intermediate Substance Name]*

285 This section is typically not needed for chemical entities. If applicable, storage information
286 may be provided.

287 For biological starting/source materials, information on the container closure system, stability
288 storage conditions, retest period/shelf life, and shipping conditions should be included, as
289 appropriate. When applicable, a description of the cold chain logistics should be provided.

290 **2.3.3.RM Raw Materials**

291 *[Raw Material Name] [Drug Substance Name] [Manufacturer] [Intermediate Substance Name]*

292 This section should include information on raw materials used in the drug substance and
293 substance intermediate manufacturing processes. Information on multiple raw materials may
294 be presented in a single tabular format, as appropriate.

295 **2.3.3.RM.D Description**

296 *[Raw Material Name] [Drug Substance Name] [Manufacturer] [Intermediate Substance Name]*

297 This section should include information on the raw materials (e.g., name, where in the process
298 it is used, function).

299 **2.3.3.RM.M Manufacture**

300 *[Raw Material Name] [Drug Substance Name] [Manufacturer] [Intermediate Substance Name]*

301 This section is typically not required for chemical raw materials. If applicable, manufacturing
302 information may be provided.

303 For biological raw materials, manufacturing and/or source information relevant to adventitious
304 agent control should be included (ICH Q5A).

305 **2.3.3.RM.C Control**

306 *[Raw Material Name] [Drug Substance Name] Manufacturer] [Intermediate Substance Name]*

307 The applicant should refer to compendia or provide specifications for raw materials in line with
308 the control strategy (ICH Q11). For biological raw materials, information essential to the
309 control of adventitious agents of the materials should be included, as appropriate (ICH Q5A).
310 If applicable, the applicant should discuss control of adventitious agents in 2.3.4.IN.2.2.

311 **2.3.3.RM.S Storage**

312 *[Raw Material Name] [Drug Substance Name] [Manufacturer] [Intermediate Substance Name]*

313 For chemical raw materials, this section is typically not required. For biological raw materials,
314 this section may include storage information.

315 **2.3.3.EX Excipients**

316 *[Excipient Name] [Drug Product Name] [Manufacturer]*

317 This section should include information on excipients used in the manufacture of the finished
318 dosage form.

319 For compendial excipients, information may be presented in a single tabular format including
320 their function and reference to relevant standards.

321 For novel excipient(s), this section should include full details of description, manufacture,
322 control, and storage, with cross-references to supporting safety data (nonclinical and/or
323 clinical).

324 **2.3.3.EX.D Description**

325 *[Excipient Name] [Drug Product Name] [Manufacturer]*

326 For novel excipients or non-compendial excipients that might directly impact drug product
327 performance, (e.g., release controlling agents, adjuvants), a detailed description should be
328 provided in this section. If applicable, the description should include the characteristics that
329 correlate to the drug product's CQA. If the excipient is formulated or consists of a mixture of
330 compounds, the qualitative and, whenever possible, quantitative composition should be
331 specified.

332 **2.3.3.EX.M Manufacture**

333 *[Excipient Name] [Drug Product Name] [Manufacturer]*

334 Where appropriate, e.g., for novel excipients, this section should include a general outline of
335 the manufacturing process and controls relevant for the CQAs of the drug product.

336 **2.3.3.EX.C Control**

337 *[Excipient Name] [Drug Product Name] [Manufacturer]*

338 For compendial excipients, specifications additional to the compendia reference(s) should be
339 included, as appropriate.

340 For novel or non-compendial excipients, this section should include specifications with a cross-
341 reference to 2.3.3.AP, as appropriate.

342 For biological excipients, information on the control of adventitious agents should be included,
343 as appropriate (ICH Q5A). If applicable, the applicant should discuss control of adventitious
344 agents in 2.3.4.IN.2.2.

345 **2.3.3.EX.S Storage**

346 *[Excipient Name] [Drug Product Name] [Manufacturer]*

347 Where applicable, e.g., for novel excipients, this section should include information on the
348 container closure system, storage conditions, and retest period/shelf life.

349 **2.3.3.RS Reference Standards and/or Materials**

350 *[Reference Standard Name] [Manufacturer] [Drug Substance Name] [Drug Product Name]*

351 This section should include information on the reference standard(s) and/or material(s) used
352 for testing of drug substance, drug product, substance intermediate, and product intermediate,
353 when necessary (ICH Q6A/Q6B). Information on multiple reference standards may be
354 provided in a single tabular format, as appropriate.

355 **2.3.3.RS.D Description**

356 *[Reference Standard Name] [Manufacturer] [Drug Substance Name] [Drug Product Name]*

357 This section should include nomenclature and structural features, as appropriate (ICH
358 Q6A/Q6B).

359 **2.3.3.RS.M Manufacture**

360 *[Reference Standard Name] [Manufacturer] [Drug Substance Name] [Drug Product Name]*

361 For chemical reference standards and/or materials, this section is typically not required. For
362 biological in-house reference materials, this section should include manufacturing/purification
363 information (e.g., process description or a cross-reference to relevant sections), if applicable
364 (ICH Q6A/Q6B).

365 **2.3.3.RS.C Control**

366 *[Reference Standard Name] [Manufacturer] [Drug Substance Name] [Drug Product Name]*

367 This section should include a list of specifications with references to compendial methods or
368 cross-references to 2.3.3.AP. For biological in-house reference materials, additional
369 information such as calibration (against e.g., primary/international standards) or qualification
370 procedures may be provided, if applicable (ICH Q6A/Q6B).

371 **2.3.3.RS.S Storage**

372 *[Reference Standard Name] [Manufacturer] [Drug Substance Name] [Drug Product Name]*

373 For biological in-house reference materials, this section should include the storage conditions,
374 use period, and the container closure system.

375 **2.3.3.DP Drug Products**

376 *(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]*

377 The applicant should organise information in this section in a systematic manner to include
378 core quality information for each drug product constituent (e.g., isotope, lyophilized powder
379 and diluent/solvent). This section may be repeated as needed.

380 **2.3.3.DP.D Description**

381 *(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]*

382 This section should include a description of the finished dosage form including its type,
383 qualitative and quantitative composition, and overages/overfills, if applicable. A list of all
384 excipients with their name, function, references to their quality standards, and their amounts
385 on a per-unit basis should be provided in a tabular format. Where relevant, this section should
386 include the reference strength of the active moiety/entity if it differs from the drug substance
387 strength. A brief description of the container closure system (primary and functional secondary
388 packaging) used for the finished dosage form should be included. Any special design features
389 of the drug product should be identified (ICH Q8).

390 **2.3.3.DP.M Manufacture**

391 *(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]*

392 When multiple manufacturers are involved in the manufacturing of the drug product, the
393 applicant may repeat some of these subsections as needed. If the information for each
394 manufacturing site is the same, there is no need to repeat the sections.

395 **2.3.3.DP.M.1 Batch formula**

396 This section should include a definition of the batch size and the batch formula for batches
397 (ICH Q8, Q13). A batch formula should include a list of all components of the finished dosage
398 form to be used in the manufacturing process; their amounts on a per batch basis, including any
399 overages; and a reference to their quality standards.

400 **2.3.3.DP.M.2 Description of the manufacturing process**

401 This section should include sufficient information on the drug product commercial
402 manufacturing process along with a flow diagram/process schematic, which represents the
403 sequence of unit operations and the scale of production, including product intermediate(s), if
404 applicable. The diagram should indicate steps where materials enter and/or exit the process and
405 points of sampling at which IPCs, testing of intermediates, or final product controls are
406 conducted. If applicable, the applicant should identify the unit operations conducted in batch
407 mode or in a continuous manufacturing process, any process models utilised, and describe the
408 proposed design space, if any (ICH Q8, Q13).

409 When an integral device is utilised, the drug product manufacturing process description should
410 include the assembly steps of the drug product and medical device/medical device component.

411 A list of the type of equipment used should be included. For major equipment that has an impact
412 on product quality, additional information, such as design, operating principle, and/or size
413 should be provided.

414 For products intended to be sterile, the method of sterilisation for the drug product (including
415 primary packaging material sterilisation, if applicable) along with appropriate acceptance
416 criteria should be included. If the primary packaging is a pre-sterilised device, the applicant

417 should include information about sterilisation in 2.3.3.MD.M.

418 If applicable, reprocessing steps should be identified and included in the process flow diagram.

419 *2.3.3.DP.M.3 Process controls*

420 This section should include process parameters and IPCs that are essential for ensuring that a
 421 drug product of required quality is produced consistently. The section should include associated
 422 test methods (with cross-references to relevant Analytical Procedures sections) and control
 423 ranges/acceptance criteria, organised per unit operation. When models are associated with
 424 process controls of the drug product, the applicant should present information of the models
 425 used in 2.3.3.AP.

426 **2.3.3.DP.C Control**

427 *(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]*

428 This section should include the specification(s) for the drug product, including tests, name of
 429 the analytical procedures, and acceptance criteria for both release and shelf life with applicable
 430 standards/pharmacopeia(s). Cross-references to relevant Analytical Procedures sections should
 431 be provided, including any proposed RTRT approach (ICH Q6A/Q6B, Q8, Q14, M7).

432 When models are associated with the analytical procedures for release and/or stability testing
 433 of the drug product, this section should include a description/identification of the models used
 434 in 2.3.3.AP.

435 For the controls performed on the product after transformation (e.g., appearance after
 436 reconstitution) and for the controls related to device functionalities, the appropriate release and
 437 shelf-life specifications should be included in this section. Specifications that are not part of
 438 the release or stability testing of drug product, e.g., for compatibility/in-use after
 439 transformation, should be included in 2.3.3.PH.C.

440 **2.3.3.DP.S Storage**

441 *(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]*

442 *2.3.3.DP.S.1 Container closure system*

443 This section should include information about the container closure system including materials
 444 of construction proposed for bulk product, if applicable, and drug product (ICH Q8).
 445 Specifications for primary packaging material and functional secondary packaging material
 446 should be included.

447 *2.3.3.DP.S.2 Stability, storage conditions, and shelf life*

448 This section should include information about the proposed storage conditions and shelf life.
 449 This storage information may cover in-use, short-term excursions, and shipping. The
 450 information for each of the proposed container closure system(s) used for bulk product (if
 451 applicable) and drug product should be provided. The post-approval stability protocol and
 452 stability commitment may be provided (ICH Q1/Q5C).

453 For biologics, if applicable, this section should include traceability (chain of custody and chain
 454 of identity).

455 **2.3.3.PI Product Intermediates, if Applicable**

456 *(Product Intermediate Name) [Manufacturer] [Drug Product Name]*

457 This section should provide information for product intermediates with established
458 specifications. The applicant should provide information for Description, Control and Storage
459 as applicable.

460 **2.3.3.PI.D Description**

461 *(Product Intermediate Name) [Manufacturer] [Drug Product Name]*

462 This section should include identification and composition (if applicable), of each product
463 intermediate, including a list of all excipients with their name, function, and references to their
464 quality standards, to the same level of detail as in 2.3.3.DP.D.

465 **2.3.3.PI.M Manufacture**

466 *(Product Intermediate Name) [Manufacturer] [Drug Product Name]*

467 If the product intermediate is manufactured separately, this section should include the batch
468 formula, which includes a list of all components of the product intermediate, their amounts,
469 and a reference to their quality standards.

470 The applicant may provide the Manufacture information integrated into section 2.3.3.DP.M or
471 separately, if deemed necessary (e.g., different manufacturer, different manufacturing process)
472 and the content should align with 2.3.3.DP.M, as applicable.

473 **2.3.3.PI.C Control**

474 *(Product Intermediate Name) [Manufacturer] [Drug Product Name]*

475 This section should include specification(s) for the product intermediate and references to
476 relevant analytical procedures. If applicable, a description of any proposed RTRT approach
477 should be included (ICH Q6A/Q6B, Q8, Q14).

478 **2.3.3.PI.S Storage**

479 *(Product Intermediate Name) [Manufacturer] [Drug Product Name]*

480 This section should include information regarding the container closure system, stability,
481 storage conditions, holding time/shelf life to the same level of detail as under each
482 corresponding heading in 2.3.3.DP.S. Additionally, shipping conditions may be provided.

483 **2.3.3.MD Medical Devices, if Applicable**

484 *(Medical Device Name) [Manufacturer]*

485 This section should be used when regional requirements mandate that the elements pertaining
486 to the medical device should be submitted as part of a medicinal product application. This may
487 include cases where:

- 488 • the medical device and/or device part and the medicinal product form an integral
489 product intended exclusively for use in the given combination, which is not reusable
490 and where the action of the medicinal product is principal;
- 491 • the medical device is packed together with the medicinal product (sometimes called
492 “co-packaged”);
- 493 • the product information refers to a specific medical device to be used with the medicinal
494 product, and the medical device is obtained separately by the user of the medicinal
495 product (sometimes called “referenced”).

This section should include information relevant for the device or the device constituent(s) before it encounters the medicinal product. The applicant should place information relating to the device once combined with the medicinal product (e.g., compatibility of the device with the formulation or changes in the device design and operating characteristics during the medicinal product development) in the relevant sections as follows:

- In the *DP* (drug product) section in case of an integral device if no transformation is required.
- In the *PM* (packaged medicinal product) section in case of co-packaged or referenced device, leading to the medicinal product being a multiconstituent product.
- In the *PH* (pharmaceutical product after transformation) section in case of an integral, co-packaged, or referenced device intended to be used in combination with the pharmaceutical product after transformation.

If applicable, this section should include confirmation that the device has been assessed and authorised for use as medical device. Such confirmation may replace part or most of the information described in these medical device sections.

Software information should be included in this section when information on medical device software is required per regional regulations. Software in scope of this guideline may include, for example, software that is classified as an integral medical device, or as components or accessories of a medical device.

2.3.3.MD.D Description

(Medical Device Name) [Manufacturer]

This section should include a description of the medical device covering aspects relevant for the medicinal product quality, safe use, and performance. This may include dimensions, principles of operation, functionalities, and/or a visual representation of the device. If applicable, the critical components or accessories of the device should also be described.

If applicable, this section should include the device risk classification according to the (regional) regulatory classification system, as well as evidence (e.g., certificate) that the device has been assessed and authorised for use as medical device in compliance with regional requirements.

In case of use of software as a medical device, the name, major version, and description of its purpose may be provided.

2.3.3.MD.M Manufacture

(Medical Device Name) [Manufacturer]

This section may include a description of the manufacturing process of the device or device parts. A list of process parameters impacting the device's performance, with their associated values, should be provided. For devices intended to be sterile, an appropriate method of sterilisation should be mentioned.

2.3.3.MD.C Control

(Medical Device Name) [Manufacturer]

This section should include the specifications of the medical device or device constituent parts that are not fully assembled into a device. This may include dimensions and operating conditions.

538 If applicable, this section should include software specifications appropriate to confirm
539 compliance with regulatory, cybersecurity, and interoperability requirements.

540 **2.3.3.MD.S Storage**

541 *(Medical Device Name) [Manufacturer]*

542 If applicable, this section may include the shelf life/re-test period, storage conditions, and
543 packaging of the medical device.

544 **2.3.3.PM Packaged Medicinal Products for multiconstituent products, if Applicable**

545 *(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]*

546 This section should include information about the marketing pack(s) for medicinal products
547 that contain constituents (individually packaged in primary container) and that are subsequently
548 packaged together in a secondary container or in a unit as a marketing pack. For example, a
549 vial with a powder for solution may be packaged together with a syringe, or several primary
550 packaged drug products may be packaged together in a marketing pack.

551 **2.3.3.PM.D Description**

552 *(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]*

553 This section should include the configuration description. A description of functional
554 secondary packaging may be provided.

555 **2.3.3.PM.M Manufacture**

556 *(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]*

557 If the secondary packaging process directly affects product quality, this section should include
558 a description of the process for packaging the separately packaged constituents into the final
559 container, as appropriate.

560 **2.3.3.PM.C Control**

561 *(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]*

562 This section may include release and shelf-life specifications. If information about any
563 separately packaged constituent is not included in 2.3.3.DP or 2.3.3.MD section, the
564 specifications for this separately packaged constituent should be included in this section.

565 **2.3.3.PM.S Storage**

566 *(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]*

567 **2.3.3.PM.S.1 Container closure system**

568 If functional secondary packaging is applied, specifications should be provided.

569 **2.3.3.PM.S.2 Stability, storage conditions, and shelf life**

570 This section should include the storage conditions and shelf life, if different from those of its
571 individual constituents, cross-referencing the storage section(s) of 2.3.3.DP and/or 2.3.3.MD,
572 as appropriate. Information for in-use and shipping may be provided. The post-approval
573 stability protocol and stability commitment may be provided (ICH Q1).

574 **2.3.3.PH Pharmaceutical Product after transformation, if Applicable**

575 *(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]*

576 This section should include information in situations where the finished dosage form needs

577 transformation into its administrable dosage form (e.g., dilution, dissolution, dispersion,
578 suspension, or reconstitution).

579 **2.3.3.PH.D Description**

580 *(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]*

581 This section should include the details of transformation of the drug product including
582 composition or composition range of pharmaceutical product after transformation, as
583 appropriate.

584 **2.3.3.PH.M Manufacture**

585 *(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]*

586 Not applicable.

587 **2.3.3.PH.C Control**

588 *(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]*

589 This section is intended to cover additional controls that may be appropriate after product
590 transformation and prior to use, or for tests conducted to confirm in-use quality requirements.

591 This section may include tests that are not conducted at the time of release or on stability and
592 do not need to be part of routine tests (such as compatibility/in-use after transformation).

593 The applicant should not duplicate information for release and stability specification of
594 parameters to be performed for pharmaceutical product after transformation that is already
595 mentioned in 2.3.3.DP.C.

596 **2.3.3.PH.S Storage**

597 *(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]*

598 **2.3.3.PH.S.1 Stability, storage conditions, and shelf life**

599 This section may include the in-use storage condition and in-use period, as appropriate. The
600 stability protocol or a summary in case of any planned post-approval stability study may be
601 included.

602 **2.3.3.AP Analytical Procedures**

603 *(Analytical Procedure Name or code) [Purpose] [Material Type]*

604 This section should be used to identify all non-compendial procedures by, at a minimum, the
605 name or the code of each procedure, the material(s) for which it is used, and the purpose of the
606 test. Compendial procedures should be referenced where they are used (e.g., in control sections
607 of the different materials), however compendial procedures that are adjusted by the applicant
608 are expected to be presented in this section. An overview table containing all non-compendial
609 procedures and adjusted compendial procedures used in the control strategy (e.g., release,
610 stability, IPC) for the different materials may be provided.

611 For each procedure, this section should include an appropriate description or tabulated version
612 of the analytical procedures according to principles defined in ICH Q14. When models for
613 multivariate analytical procedures are associated with the analytical procedures, a description
614 of that model should also be presented. When RTRT is used, the description of the
615 corresponding analytical procedure should be included.

616 The level of detail should be commensurate with the nature and risk of the material.

617 **2.3.3.FA Facilities**

618 *[Manufacturer]*

619 This section should include the name, address, and responsibility of each manufacturer,
620 including contractors, and each proposed production site or facility involved in manufacturing
621 and testing of drug substance, drug substance intermediates, drug product, and drug product
622 intermediates. Regional guideline may describe expectations for the content of this section in
623 more detail.

624 **2.3.4 Development Summary and Justification**

625 This section should describe how the drug substance and product, their components, if
626 applicable, and manufacturing process were developed, including the main choices made
627 throughout the development. This section should include science- and risk-based justifications,
628 including discussion of the proposed commercial process and control strategy, and when ICH
629 Q12 is applied, the justification of ECs and reporting categories, if applicable. The applicant
630 may include a discussion of relevant prior knowledge, such as platform technology experience,
631 as well as knowledge or experience from other similar products, available to the applicant
632 together with justifications of its applicability to the product in the marketing authorisation
633 application. The content of this section is supportive. The applicant may amend or supplement
634 the information due to post-approval submissions. Information in Module 3 may be cross-
635 referenced to support the discussion as needed.

636 The 2.3.4 sections of a drug product and drug substance will also cover the materials used in
637 drug substance/drug product manufacture (e.g., raw materials, excipients, substance
638 intermediate, and product intermediates). In cases where one or more of these materials has
639 undergone a separate development, the applicant may use a separate section 2.3.4 for this
640 material with the corresponding DMCS structure (e.g., 2.3.4.SI Substance Intermediate,
641 2.3.4.RM Raw Material, 2.3.4.EX Excipients, or 2.3.4.PI Product Intermediate). Subsections
642 and content should match 2.3.4.DS/DP sections, as appropriate. The applicant should not repeat
643 the information in section 2.3.4.DS or 2.3.4.DP.

644 **2.3.4.IN Integrated Development and Justifications**

645 This section is used for the justification of topics when a holistic discussion across several parts
646 of the dossier is advantageous, e.g., across drug substance to drug product. The corresponding
647 Core Quality Information is provided in relevant subsections of 2.3.3 and the corresponding
648 data and supportive information in Module 3.2, where the topic is addressed as specified below.

649 **2.3.4.IN.1 Overview of changes during development**

650 This section may present a tabular overview of the changes during development, the reason for
651 each change, and the batches used for clinical and nonclinical studies. Appropriate
652 justifications should be included in relevant subsections of 2.3.4 with data and supportive
653 information in Module 3.2. The applicant should provide cross-references to the location of
654 studies in other sections or modules of the CTD that are used to assess the impact of changes
655 on the drug substance(s) and corresponding drug product(s) (ICH Q5E, Q8, Q9, Q10, Q11).

656 **2.3.4.IN.2 Integrated discussions**

657 This section contains end-to-end justifications, as appropriate. The applicant can apply the
658 DMCS structure as appropriate. The applicant should not repeat justifications included here in

659 2.3.4.DS or 2.3.4.DP.

660 **2.3.4.IN.2.1 Integrated justifications of extractables and leachables**

661 This section should include a comprehensive summary of the assessment of the potential risks
662 associated with extractables and leachables. Information submitted in this section should be
663 cross-referenced to the following: 1) relevant subsections in 2.3.4 which provide justification
664 for the selection of materials, manufacturing systems, container closure systems, and device
665 components; 2) relevant subsections of 2.3.3 where the actual controls are delineated; 3)
666 appropriate Module 3.2 subsections which contain supportive information and data; and 4)
667 appropriate Module 4 sections providing safety data and supportive information.

668 **2.3.4.IN.2.2 Integrated justifications of control of adventitious agents**

669 This section should describe the integrated justification assessing the risk of adventitious agents
670 (ICH Q5A, Q5D, Q6A/Q6B). Development work, including testing done during development
671 (e.g., viral clearance studies) should be discussed. If applicable, the results of clearance studies
672 as part of the justification of the integrated control strategy of adventitious agents should be
673 summarised. The integrated justification should cross-reference the specific quality
674 requirement and controls for raw/starting/source materials and the manufacturing process
675 included in 2.3.3. The data and information from the studies should be provided in the
676 corresponding materials subsection in Module 3.2.

677 For non-viral adventitious agents, an integrated justification on the avoidance and control of
678 these agents, such as transmissible spongiform encephalopathy agents, bacteria, *Mycoplasma*,
679 and fungi should be provided. This justification may include, for example, certification and/or
680 testing of raw materials, excipients, or other materials, as well as justification around relevant
681 control of the manufacturing process, as appropriate for the material, process, and agent.

682 For viral adventitious agents, an integrated justification on the avoidance and control of viral
683 contamination should be provided. Viral safety studies should demonstrate that the materials
684 used in manufacturing are considered safe, and that the approaches used to test, evaluate, and
685 eliminate the potential risks during manufacturing and material sourcing are suitable.

686 **2.3.4.IN.2.3 Development and justifications for products without a defined and/or isolated drug**
687 **substance**

688 This section should summarise the development and justification of the commercial
689 manufacturing process and its control strategy for products without a defined and/or isolated
690 drug substance (e.g., integrated drug substance and drug product continuous manufacturing or
691 some ATMPs). The applicant should apply the DMCS structure and include all relevant
692 descriptions and justifications, such as those related to cell line or starting materials,
693 manufacturing (including an overview and the process design), and formulation. The applicant
694 should provide justification for viral vectors used for *ex vivo* genome modification of cellular
695 ATMPs in 2.3.4.SI. The applicant should not repeat justifications included in this section in
696 2.3.4.DS or 2.3.4.DP.

697 The applicant should include CQI in the relevant 2.3.3 section. For example, for cellular ATMP
698 that are gene-modified with a viral vector, viral vector CQI should be included in 2.3.3.SI and
699 information on description, manufacturing, and formulation of the product in 2.3.3.DP. The
700 data and supporting information should be included in the corresponding 3.2 section (ICH
701 Q3A-Q3E, Q5A-Q5E, Q6A/Q6B, Q13, M7).

702 **2.3.4.IN.2.4 Integrated justifications of specific items (Optional)**

703 The applicant may choose to justify the control strategy in this section where an end-to-end
704 justification is of significant advantage. The applicant may repeat this section for specific uses
705 (e.g., integrated justification of specifications, mutagenic impurities, residual solvents, and
706 elemental impurities). The CQI or data and supportive information should be provided in the
707 corresponding material subsections in 2.3.3 or 3.2, respectively (ICH Q1/Q5C, Q3A-Q3E,
708 Q5A-Q5E, Q6A/Q6B, M7).

709 **2.3.4.IN.3 Equivalency, similarity or sameness with a reference product**

710 **2.3.4.IN.3.1 Summary and Justifications of analytical and in vitro similarity with a reference**
711 **product, if Applicable**

712 The applicant should explain the choice of reference product, including justification if samples
713 of the reference product have been acquired from another region, when such an approach is
714 acceptable according to regional requirements.

715 For a generic product or other follow-on to a chemical entity (e.g., abridged/abbreviated
716 application), an overview of how the *in vitro* equivalency with the reference product is
717 demonstrated should be included. It may include biowaiver approaches. Details should be
718 provided in 2.3.4.DP.D, 2.3.4.DP.M and/or in 3.2.DP, as appropriate.

719 For a biosimilar product, the applicant should delineate the strategy for biosimilarity
720 assessment, provide a summary of the results of the biosimilarity studies, and justify
721 biosimilarity with the reference product. Data and information should be provided in 3.2.DP.D.

722 **2.3.4.IN.3.2 Summary and Justifications of sameness with a product approved in a reference country,**
723 **if a reliance procedure is used**

724 The applicant should discuss and declare sameness of the medicinal product with the product
725 approved in the reference country, according to regional guidelines. The applicant should
726 explain and justify any difference.

727 **2.3.4.DS Drug Substances**

728 *(Drug Substance Name) [Manufacturer]*

729 The information for each drug substance or manufacturing site should be organised following
730 the guidelines specified in this section and may be repeated in this section as necessary to
731 accommodate multiple drug substances or manufacturing sites. If the information for each
732 manufacturing site is the same, there is no need to repeat the sections.

733 **2.3.4.DS.D Description**

734 *(Drug Substance Name) [Manufacturer]*

735 A summary of the studies performed to characterise and confirm the drug substance structure
736 and its general properties, including physicochemical and biological properties should be
737 provided in this section. The level of detail should be commensurate with the nature of the
738 substance, whereby a greater level of detail may be appropriate for highly complex substances.

739 **2.3.4.DS.M Manufacture**

740 *(Drug Substance Name) [Manufacturer]*

741 *2.3.4.DS.M.1 Development of manufacturing process and process controls*

742 This section should include information on how the manufacturing process was developed to
743 establish the commercial manufacturing process capable of consistently producing drug
744 substance of the intended quality (ICH Q11).

745 For biologics, the proposed batch scale up may be discussed, as applicable (ICH Q11). This
746 section should describe the risk assessment approach(es) used and summarize how the
747 conclusions from the risk assessment(es) were used to justify the manufacturing process
748 development (ICH Q11).

749 Information should be included if modelling is used as part of the manufacturing and process
750 controls.

751 For sterile drug substances, the applicant should justify the chosen method of sterilisation.

752 For biological drug substances, the applicant should discuss and justify clearance steps (for
753 product- and process-related impurities). Viral clearance studies should be discussed in
754 2.3.4.IN.2.2.

755 This section should include information on the development and characterisation of the process
756 controls, including how the process parameters and IPCs and their ranges were identified (ICH
757 Q11). Information should be included if modelling is used as part of the control strategy.

758 When an enhanced approach is used, this section should discuss the impact of the
759 manufacturing process on the CQAs, understanding of the relationship between input and
760 outputs, justification of process ranges/acceptance criteria for inputs and outputs, and design
761 space, if applicable (ICH Q11).

762 *2.3.4.DS.M.2 Changes during manufacturing process development*

763 This section should discuss significant changes to the manufacturing process of the drug
764 substance used to produce nonclinical / clinical batches (as appropriate) and batches proposed
765 for commercial distribution (ICH Q11).

766 *2.3.4.DS.M.3 Comparability for multiple manufacturing sites*

767 In the case of more than one proposed commercial manufacturing site, this section should
768 provide comparative information and discuss the impact of any differences between the sites
769 on the drug substance quality and consistency.

770 *2.3.4.DS.M.4 Summary of process validation or evaluation studies*

771 This section should include summaries and conclusions of the process validation and or
772 evaluation studies. Process validation for non-sterile chemical entities may not be necessary at
773 the time of application.

774 This section should include justification for processes where manufacturing equipment is
775 intended to be reused.

776 If raw materials (e.g., solvent) are intended to be recycled or regenerated, a justification should
777 be included.

778 For biologics, a justification for holding times and storage conditions for intermediates should

779 be included (ICH Q5C).

780 A justification for any reprocessing steps for the product type should be included according to
781 ICH Q7.

782 **2.3.4.DS.C Control**

783 *(Drug Substance Name) [Manufacturer]*

784 **2.3.4.DS.C.1 Control of impurities**

785 For chemical entities, this section should summarise the actual and potential impurities most
786 likely to occur during the synthesis, purification, and storage of the drug substance, with a
787 comprehensive risk assessment. Any potential impurity that may impact the quality of the drug
788 substance, including those originating from starting/source materials, raw materials, and
789 substance intermediates, should be discussed as part of the risk assessment. The applicant
790 should also cross-reference the associated data provided in 3.2.IM and provide the rationale for
791 the reporting and control of impurities (ICH Q3A, Q3C, Q3D, M7). If an integrated discussion
792 is needed, the applicant may consider using 2.3.4.IN.2.4.

793 For biologics, information about product and process-related impurities should be provided
794 (ICH Q6A/Q6B). For the control of product and process-related impurities, subsections for
795 each identified impurity may be included.

796 **2.3.4.DS.C.2 Batch analysis**

797 This section should include a tabulated overview of batches, listing the batch number, batch
798 size/scale, date of manufacture, manufacturing site, manufacturing process (biologics), and use
799 (e.g., stability, nonclinical, and clinical). A discussion on conformance to specifications and
800 justification of trending should be included, as appropriate.

801 **2.3.4.DS.C.3 Justification of specifications**

802 This section should include justification for release and stability specifications, including the
803 rationale for the quality attributes to be tested and CQAs not tested, if any. Compliance to any
804 standard/pharmacopeia(s) should be specified. The rationale for skip-testing/non-routine
805 testing for the drug substance should be included.

806 A rationale for relevant changes to specifications throughout development should be provided,
807 which may include a reference to other sections discussing development aspects (e.g.,
808 2.3.4.DS.M, 2.3.4.AP), as appropriate.

809 If RTRT approach is adopted, a justification for the approach should be included (ICH
810 Q6A/Q6B, Q11, Q13, Q14, M7).

811 **2.3.4.DS.S Storage**

812 *(Drug Substance Name) [Manufacturer]*

813 **2.3.4.DS.S.1 Container closure system**

814 This section should include justification for the proposed container closure system, including
815 primary and functional secondary packaging components that are critical to drug substance
816 quality.

817 The justification should include reasons for the choice of materials. It should also address safety

818 of materials of construction and compatibility of the material(s) of construction with the drug
819 substance, including potential interactions between drug substance and container (e.g., sorption
820 to container and leaching) cross-referencing 2.3.4.IN.2.1.

821 *2.3.4.DS.S.2 Stability, storage conditions, and retest period/shelf life*

822 An overview of the stability and a justification for storage condition and retest period/shelf life
823 for the proposed container closure system of the drug substance should be provided. The
824 approach for calculating the drug substance retest period/shelf life should be justified. If
825 extrapolation is proposed, this section should include a justification for the approach used to
826 calculate the drug substance retest period/shelf life (ICH Q1).

827 A summary of the studies conducted and the conclusions of these studies with respect to storage
828 conditions and shelf life should be provided (ICH Q1).

829 For biological bulk material and drug substance the shipping conditions should be justified.

830 **2.3.4.SM Starting/Source Materials**

831 *[Starting Material Name] [Drug Substance Name] [Intermediate Substance Name]*

832 This section should be used as needed to provide justifications for starting materials in
833 accordance with relevant guidelines (ICH Q5A, Q5B, Q5D, Q11, Q11 Q&A). The DMCS
834 structure may be applied, as appropriate.

835 **2.3.4.SM.D Description**

836 *[Starting Material Name] [Drug Substance Name] [Intermediate Substance Name]*

837 This section should include information on selection of the starting material(s), as appropriate
838 (ICH Q11 Q&A).

839 For cell banks, this section should include information on the source of the cell substrate and
840 analysis of the expression construct used to genetically modify cells and incorporated into the
841 initial cell clone used to develop the MCB (ICH Q5B, Q5D).

842 **2.3.4.SM.M Manufacture**

843 *[Starting Material Name] [Drug Substance Name] [Intermediate Substance Name]*

844 For chemical entities starting materials that are not commercially available, this section should
845 include a manufacturing process flow of the starting material, if applicable, to help justify the
846 controls applied to the starting material (ICH Q11 Q&A).

847 For biological starting materials, this section should include information on the establishment
848 of the MCB, the WCB, or the virus seed/bank system, as applicable (ICH Q5B, Q5D).

849 **2.3.4.SM.C Control**

850 *[Starting Material Name] [Drug Substance Name] [Intermediate Substance Name]*

851 This section should include a justification of specifications for starting materials, as applicable
852 (ICH Q5B, Q5D, Q11, Q11 Q&A).

853 **2.3.4.SM.S Storage**

854 *[Starting Material Name] [Drug Substance Name] [Intermediate Substance Name]*

855 For biological starting materials, justifications for storage/shipping conditions, as well as
856 proposals for monitoring of stability should be included (ICH Q5B, Q5D).

2.3.4.RS Reference Standards and/or Materials

(Reference Standard Name) [Manufacturer]

This section should include information on the characterisation of reference standards/materials. If distinct reference standards/materials are developed for process/product related impurities, their appropriateness should be discussed. For biological in-house reference materials, this section should summarize results of calibration or qualification of current and historical in-house reference materials, as well as a justification of the appropriateness of the storage conditions, use period, and container closure system, if applicable. The applicant may apply the DMCS structure as appropriate.

2.3.4.DP Drug Products

(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]

The applicant may repeat this section as needed, for example, to include the development information of each drug product or a diluent/solvent that is part of the packaged medicinal product.

2.3.4.DP.D Description

(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]

2.3.4.DP.D.1 Components of the drug product

This section should discuss the development studies supporting the choice of excipients, including their concentration, amounts, quality, and functional characteristics that can influence the drug product performance relative to their respective functions.

The compatibility between the drug substance(s) and excipients should be discussed. Additionally, key physicochemical characteristics of the drug substance may be discussed, as appropriate, such as water content, solubility, particle size distribution, polymorphic or solid-state form (with a cross-reference to specific information provided under 2.3.4.DS.D) that can influence the drug product performance.

When a device is used in direct contact with the drug product, either as part of or as the primary container closure system, the choice of the device and its compatibility with the formulation (integral devices) should be discussed.

2.3.4.DP.D.2 Formulation development

This section should include information on the development studies conducted to establish the dosage form and the formulation (ICH Q8, Q9). The development of the dosage form and formulation for drug product, taking into consideration the proposed route of administration and usage should be discussed. Where relevant, this section should include the reference strength or chemical or physical form (e.g., salt form, stereoisomer or polymorphic form) of the active moiety/entity if it differs from the drug substance strength or form. If applicable, the rationale for any special design features and how they affect the drug product should be discussed.

A discussion of any overages in the formulation should be included with a justification concerning the safety and efficacy of the product in terms of the reason and amount of overage, if applicable.

897 *2.3.4.DP.D.3 Comparability during formulation and product development*

898 This section should discuss differences between clinical formulations and the proposed
899 commercial formulation (i.e., composition, dosage form) and provide justification to support
900 the level of change. Where applicable, the bridging strategy, including results of comparative
901 *in vitro* studies (e.g., dissolution) or a summary and reference to comparative *in vivo* studies
902 (e.g., bioequivalence), should be provided as appropriate (ICH M9, M13).

903 This section may include a discussion of any change in the device design and operating
904 characteristics (for integral devices) during product development. It should cover how these
905 changes may impact safety, and/or performance and/or instructions for use of the overall
906 product. Where relevant, it should explain any differences between the study device and its
907 commercial form.

908 *2.3.4.DP.D.4 Physicochemical and biological properties of drug product*

909 This section may include physicochemical and biological properties relevant to the
910 performance of the drug product, such as pH, ionic strength, dissolution, redispersion,
911 reconstitution, particle size distribution, aggregation, polymorphism, rheological properties,
912 biological activity or potency, and/or immunological activity.

913 *2.3.4.DP.D.5 Microbiological attributes*

914 As appropriate, this section should discuss the microbiological attributes of the proposed
915 dosage form, including, for example, the selection and effectiveness of preservative systems in
916 products containing antimicrobial preservatives.

917 **2.3.4.DP.M Manufacture**

918 *(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]*

919 *2.3.4.DP.M.1 Development of manufacturing process and process controls*

920 This section should provide information on how the manufacturing process was developed to
921 establish the commercial manufacturing process capable of consistently producing drug
922 product of the intended quality. The approach(es) followed for risk assessment should be
923 described and the conclusions used to justify the manufacturing process development should
924 be summarised. The proposed batch scale up may be discussed, as applicable (ICH Q8). For
925 sterile products, the chosen method of sterilisation should be justified.

926 Information on the development and characterisation of the process controls should be
927 provided, including summaries of the studies that describe how the parameters and in-process
928 controls and their ranges were established (ICH Q8).

929 A discussion of the impact of the manufacturing process on the CQAs, understanding of the
930 relationship between the inputs and outputs, justification of process ranges/acceptance criteria
931 for inputs and outputs, and design space, if applicable, should be included when an enhanced
932 approach is used (ICH Q8).

933 If modelling is used as part of the manufacturing and process controls, relevant information
934 should be included.

935 *2.3.4.DP.M.2 Changes during manufacturing process development*

936 This section should discuss the significant changes to the manufacturing process and/or

937 manufacturing site of the drug product used to produce registration/pilot, nonclinical, clinical
938 batches, and batches intended for commercial distribution, as applicable. Information should
939 be presented in a way that facilitates comparison of the processes and the corresponding batch
940 analysis information under 3.2.DP.C (ICH Q8). The data from comparative analytical testing
941 on relevant drug product batches used to determine the impact on quality of the drug product
942 (and/or intermediate, as appropriate) should be summarised.

943 *2.3.4.DP.M.3 Comparability for multiple manufacturing sites*

944 In the case of more than one proposed commercial manufacturing site, this section should
945 provide comparative information and discuss the impact of any differences between the sites
946 on the drug product quality and consistency.

947 *2.3.4.DP.M.4 Summary of process validation or evaluation studies*

948 This section should include summaries and conclusions of the process validation and/or
949 evaluation studies, as applicable. Justification and relevant information should be provided if
950 a continuous process verification approach is used (ICH Q8).

951 Processes where manufacturing equipment (e.g., sterile filters) is intended to be reused should
952 be justified.

953 Justification for where or which raw materials (e.g., solvent) are intended to be reused,
954 recycled, or regenerated should be included.

955 Holding times and storage conditions for intermediates may be justified (ICH Q1).

956 A discussion and justification of any reprocessing procedures, including criteria for material
957 reprocessing, may be included.

958 **2.3.4.DP.C Control**

959 *(Drug Product Name) [Manufacturer] [Manufactured Dosage form] [Strength]*

960 *2.3.4.DP.C.1 Control of impurities*

961 This section should summarise the actual or potential impurities most likely to occur during
962 drug product manufacturing and storage (due to interaction with excipients, solvents and/or
963 container closure system). Any potential impurity that may impact the quality of the drug
964 product, including those originating from product intermediates, should be discussed as part of
965 the risk assessment for actual and potential impurities. The applicant should cross-reference
966 the associated data provided in 3.2.IM.

967 A summary and conclusion of the performed risk assessment may be included (ICH Q3B, Q3C,
968 Q3D, Q3E, Q5C, Q6A/Q6B, M7). If an integrated discussion is needed, the applicant may
969 consider using 2.3.4.IN.2.4.

970 *2.3.4.DP.C.2 Batch analysis*

971 A tabulated overview of the batches listing the batch number, batch size/scale, date of
972 manufacture, manufacturing site, manufacturing process, and use (e.g., stability, nonclinical,
973 clinical) should be presented. Conformance to the specification and justification of trending
974 should be discussed, as appropriate.

975 *2.3.4.DP.C.3 Justification of specifications*

976 A justification of release and stability/shelf-life specifications should be provided, including
 977 the rationale for the quality attributes to be tested and CQAs not tested, if any. Compliance
 978 with any standard/pharmacopeia(s) should be specified.

979 If applicable, the rationale for skip-testing for the drug product should be included (ICH
 980 Q6A/Q6B). Any justification for the controls performed on the product after transformation
 981 should cross-reference 2.3.4.PH.C.

982 As appropriate, this section should include information about relevant changes to specifications
 983 throughout development, which may include a reference to other sections discussing
 984 development aspects (e.g., 2.3.4.DP.M, 2.3.4.AP).

985 If RTRT approach is adopted, the approach should be justified (ICH Q6A/Q6B, Q8, Q13, Q14,
 986 M7).

987 **2.3.4.DP.S Storage**

988 *(Drug Product Name) [Manufacturer] [Manufactured Dosage form] [Strength]*

989 *2.3.4.DP.S.1 Container closure system*

990 This section should include the choice and rationale used to select the container closure
 991 system(s) for the commercial products (ICH Q8).

992 For bulk product, suitability of the container closure system may be discussed.

993 For drug product primary packaging materials, this section should discuss the suitability of the
 994 container closure system, including the suitability for the patient needs, and should justify the
 995 choice of materials with respect to the impact on product quality. The discussion should include
 996 a summary of studies performed to demonstrate the integrity of the container and closure to
 997 prevent microbial contamination and possible interactions between product and container
 998 closure system. The justification should include, for example, choice of materials,
 999 compatibility of the material(s) of construction with the finished dosage form, including
 1000 sorption to container and leaching (cross-referencing 2.3.4.IN.2.1), and safety of materials of
 1001 construction.

1002 For drug product functional secondary packaging material, the rationale for choice of
 1003 packaging material should be discussed.

1004 *2.3.4.DP.S.2 Stability, storage conditions, and shelf life*

1005 This section should provide an overview of the stability studies (including short-term studies)
 1006 and justification for storage condition/shelf life and/or holding time for each of the proposed
 1007 container closure system(s) used for the bulk product (if applicable) and for the drug product
 1008 (including for device constituents utilised as primary container closure system).

1009 If extrapolation is proposed, this section should include a justification for the approach used to
 1010 calculate the drug product shelf life (ICH Q1).

1011 Summaries and conclusions of the studies for in-use, handling, and shipping may be included.

1012 **2.3.4.MD Medical Devices, if Applicable**
1013 *(Medical Device Name) [Manufacturer]*

1014 **2.3.4.MD.D Description**
1015 *(Medical Device Name) [Manufacturer]*
1016 This section should discuss the device design. The level of detail that should be included
1017 depends on the type and complexity of the device and the risk associated with its use for the
1018 intended purpose.

1019 This section should include an assessment of biocompatibility to ensure safety according to
1020 relevant standards. Extractables study outcome should support the selection of the device, as
1021 applicable.

1022 A summary of information relating to usability/human factor studies may be presented.

1023 If applicable, software functional requirements, including software architecture, interfaces, and
1024 algorithms should be defined.

1025 **2.3.4.MD.M Manufacture**
1026 *(Medical Device Name) [Manufacturer]*
1027 Depending on the risk inherent to the device and its use in the medicinal product, this section
1028 may include a description of the manufacturing process development for the device and, where
1029 relevant, of its accessories or separate parts, including software. A discussion of the selection
1030 of materials and components used in the device may be included. If applicable, the discussion
1031 should demonstrate the compatibility of components with relevant regulatory requirements.

1032 When the device or device components undergo sterilisation before becoming a constituent of
1033 the medicinal product, a justification of the sterilisation method selection regarding its
1034 compatibility with the device materials and intended use should be provided.

1035 **2.3.4.MD.C Control**
1036 *(Medical Device Name) [Manufacturer]*
1037 The specifications applied to the device, based on the intended use, and relevant regulatory
1038 requirements should be justified, as applicable. The applicant may reference relevant standards.

1039 If applicable, a confirmation that the software was properly qualified to ensure that it performs
1040 as intended should be provided.

1041 **2.3.4.MD.S Storage**
1042 *(Medical Device Name) [Manufacturer]*
1043 Where relevant, this section may discuss information about the retest period/shelf life for the
1044 device. The applicant may define and justify packaging and storage requirements, e.g., to
1045 maintain device sterility and integrity during storage and transportation prior to its integration
1046 in the medicinal product or for co-packaged device, throughout the medicinal product shelf
1047 life.

1048 **2.3.4.PM Packaged Medicinal Products for multiconstituent products, if Applicable**
1049 *(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage form] [Strength]*

1050 **2.3.4.PM.D Description**

1051 *(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]*

1052 This section should describe the development of the final packaging configuration for
 1053 medicinal products that are packaged together in a container or in a unit (multiconstituent
 1054 products), including the justification of this configuration (e.g., suitability for the intended use),
 1055 as appropriate.

1056 The choice of the additionally packaged device, any other additionally packaged constituents,
 1057 or referenced device / administration set and their compatibility with drug product and how it
 1058 reflects on the formulation development should be discussed. Any change in the device design
 1059 and operating characteristics during the medicinal product development that may impact safety,
 1060 and/or performance and/or instructions for use of the overall medicinal product may be
 1061 discussed, explaining the differences, if any, between the study device and its commercial form.

1062 If a transformation of the drug product before administration is necessary, the applicant should
 1063 include this information in 2.3.4.PH.D.

1064 **2.3.4.PM.M Manufacture**

1065 *(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]*

1066 If the secondary packaging process directly affects product quality, this section should describe
 1067 the development of the process for packaging of the different constituents into the final
 1068 container.

1069 **2.3.4.PM.C Control**

1070 *(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]*

1071 This section may include release and stability control strategy development and justification
 1072 for the packaged medicinal product and packaged constituents (if not included in 2.3.4.DP or
 1073 2.3.4.MD).

1074 **2.3.4.PM.S Storage**

1075 *(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]*

1076 **2.3.4.PM.S.1 Container closure system**

1077 If functional secondary packaging is applied, the rationale for the choice of the packaging
 1078 material should be discussed.

1079 **2.3.4.PM.S.2. Stability, storage conditions, and shelf life**

1080 If the storage condition and shelf life differ from those of its individual components, this section
 1081 should describe the rationale for this difference. As the expiration dates of the individual
 1082 components may differ, the expiration dating rules of the packaged medicinal product should
 1083 be provided.

1084 For drug product(s) used with an additionally packaged device or any other additionally
 1085 packaged constituent (without a necessary transformation before administration), a summary
 1086 of the stability studies performed, including the conclusion of the studies should be included.

1087 This section may also include a summary and conclusions for shipping studies for the packaged
 1088 medicinal product.

1089 **2.3.4.PH Pharmaceutical Product after transformation, if Applicable**
1090 *(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]*

1091 **2.3.4.PH.D Description**
1092 *(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]*
1093 This section should discuss the development of the necessary transformation of the drug
1094 product and its justification, including any changes during development. The discussion should
1095 include the compatibility of the drug product(s) with any constituent(s) as well as diluent(s)
1096 including max/min diluting concentrations to provide appropriate and supportive information
1097 for the labelling. Additionally, this discussion may include use of alternate administration
1098 media (e.g., juice, yogurt) and/or alternate directions of use (e.g., feeding tube).

1099 If a device is used in direct contact with the pharmaceutical product after transformation, the
1100 choice of the device and its compatibility with formulation should be discussed.

1101 If applicable, any change in the device design and operating characteristics during the
1102 medicinal product development that may impact safety, and/or performance and/or instructions
1103 for use of the overall medicinal product may be discussed, explaining the differences, if any,
1104 between the study device and its commercial form.

1105 **2.3.4.PH.M Manufacture**
1106 *(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]*
1107 Not applicable.

1108 **2.3.4.PH.C Control**
1109 *(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]*
1110 This section should describe and justify the controls, such as appearance after transformation
1111 of drug product and cross-referencing release/stability/shelf-life specifications of the drug
1112 product, where relevant. To demonstrate that product quality is maintained during the intended
1113 in-use period, the controls should be justified.

1114 **2.3.4.PH.S Storage**
1115 *(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]*
1116 **2.3.4.PH.S.1 Stability, storage conditions, and shelf life**
1117 The types of studies conducted, protocols used, and the results of the studies should be
1118 summarised. This information should cover the recommended in-use storage conditions and
1119 in-use period. Similarly, this section may discuss admixture or dilution of products prior to
1120 administration, such as product added to large volume infusion containers.

1121 **2.3.4.AP Analytical Procedures**
1122 *(Analytical Procedure Name or code) [Purpose] [Material Type]*
1123 This section should include all non-compendial and adjusted analytical procedures used in the
1124 control strategy in this section.

1125 **2.3.4.AP.1 Analytical Procedure Justification**
1126 A discussion of the analytical procedure, explaining the purpose of the procedure, the analytical
1127 principles used, and justifying the suitability of the test may be presented.

1128 **2.3.4.AP.2 Analytical Procedure Validation/Qualification**

1129 This section should summarise the validation/qualification of the analytical procedures. This
1130 summary should include the tested performance characteristics, acceptance criteria, and results.

1131 **2.3.4.AP.3 Analytical Procedure Development**

1132 When development information is necessary, a summary of this information is presented here
1133 (ICH Q14 or applicable guidelines).

1134 **2.3.5 Product Lifecycle Management**

1135 The applicant should use this section to include a change summary and justification for post-
1136 approval change submissions (2.3.5.1). The Product Lifecycle Management Document (PLCM,
1137 2.3.4.2) outlines the specific plan for product lifecycle management according to ICH Q12. It
1138 includes Established Conditions (ECs), reporting categories for changes to ECs, PACMPs,
1139 and/or any post approval CMC commitments in various submission types, including those with
1140 or referencing a master file, covering initial marketing authorisation and post-approval
1141 changes.

1142 **2.3.5.1 Change Summary and Justifications**

1143 This section should be provided for each post-approval change application and include the
1144 following details:

- 1145 • A summary of the proposed change and background;
1146 • A table with present and proposed content, including listing of the updated CTD
1147 sections with cross-referencing to information in those sections;
1148 • The justification for the proposed update(s) which may be provided directly in this
1149 section with a cross-reference to 2.3.3 and Module 3.2, if applicable. Alternatively,
1150 justification for the proposed update may cross-reference the updated relevant
1151 subsection(s) of 2.3.4.

1152 **2.3.5.2 Product Life Cycle Management Document (PLCM)**

1153 **2.3.5.2.1 List of Established Conditions and Reporting Categories (Optional)**

1154 Unless otherwise specified by regional requirement, identifying ECs in CQI for a given product
1155 is not mandatory (ICH Q12). If the applicant identifies ECs according to ICH Q12 or ICH Q14,
1156 the ECs should be listed in this section, cross-referencing their detailed identification and
1157 justification in the relevant subsections of 2.3.4. ECs should be listed in a tabular format or
1158 have an unambiguous reference to which part of the information in 2.3.3 CQI is proposed as
1159 EC (e.g., for a specification). The applicant may propose ECs for all, or part of the information
1160 presented in 2.3.3 CQI. If ECs are proposed for only a part of the information in 2.3.3 CQI, the
1161 scope should be clearly defined in this section.

1162 The applicant may specify reporting categories when making a future change to an EC. If the
1163 applicant does not propose a reporting category for an EC, the change should follow regional
1164 guidelines. A detailed justification for the reporting categories should be included in the
1165 relevant subsections of 2.3.4.

1166 **2.3.5.2.2 Post-approval Quality Commitments, if Applicable**

1167 The applicant should list specified post-approval CMC commitments agreed between the MAH
1168 and regulatory authority at the time of approval in tabular format in this section. This may

1169 include, for example, additional data to be submitted post-authorisation, or protocols for studies
1170 with or without a regulatory communication. If applicable, the actual descriptions or protocols
1171 should be provided in the appropriate 2.3.3 section and referenced here.

1172 The applicant should update this section during the product lifecycle to reflect the current state
1173 of open and fulfilled commitments.

1174 ***2.3.5.2.3 List of Post-Approval Change Management Protocols, if Applicable***

1175 The applicant should list PACMPs which they intend to implement in this section.

1176 ***2.3.5.3 Content of Post-Approval Change Management Protocols, if Applicable***

1177 The applicant should include actual protocols in this section. For PACMPs involving multiple
1178 medicinal products, a cross-reference can be included as applicable.

1179 When a change is implemented, the applicant should update the relevant information in 2.3.3
1180 via regulatory communication. The applicant may also need to update or amend other sections
1181 of Modules 2 and 3.

1182 **2.3.6 Product Quality Benefit Risk (Optional)**

1183 Product Quality Benefit Risk considerations (PQBR) are expected to support the overall benefit
1184 risk discussion in 2.5 Clinical overview (M4E – Efficacy). Cross-references to other sections
1185 of the CTD may be included. The assessment of the PQBR is particularly relevant during the
1186 initial medicinal product application in some expedited review pathways (e.g., high unmet
1187 medical need). In such cases, a summary that explains the applicant's approach or rationale
1188 regarding the mitigation of the quality risks should be provided, concluding how the anticipated
1189 patient-centric benefits outweigh these residual risks or uncertainties and assessing the impact
1190 on safety and/or effectiveness of the product's usage.

1191 Potential risks associated with quality may arise from aspects of product design,
1192 manufacturing, and associated overall control strategy, or from uncertainties due to evolving
1193 level of knowledge on the product and process available at time of filing (ICH Q9).

1194 Such considerations could address the quality related aspects of the medicinal product in
1195 relation to its therapeutic context (e.g., treatment and treatment duration, therapeutic index),
1196 and potential benefits (e.g., unmet medical need). An explanation why the product quality is
1197 considered adequate should be provided, in view of the intended use of the product, ensuring
1198 that the applicable standards are met.

1199 This section may also address difficulties in adopting ICH-recommended approaches, novel
1200 strategies, or situations where clinical context significantly influences the quality strategy.

1201 This section may be updated as appropriate to reflect significant changes to the outcome of the
1202 PQBR assessment or the residual risks throughout the product lifecycle.

1203 **MODULE 3. QUALITY**

1204 **3.1 Table of Contents of Module 3**

1205 A Table of Contents for the filed application should be provided.

1206 **3.2 Body of Data**

1207 **3.2.DS Drug Substances**

1208 *(Drug Substance Name) [Manufacturer]*

1209 **3.2.DS.D Description**

1210 *(Drug Substance Name) [Manufacturer]*

1211 This section should include information supporting the drug substance structure and general
1212 properties such as physicochemical and biological properties.

1213 **3.2.DS.M Manufacture**

1214 *(Drug Substance Name) [Manufacturer]*

1215 *3.2.DS.M.1 Description of manufacturing process*

1216 In support of information provided in 2.3.3, this section should include a suitably detailed
1217 description of the commercial manufacturing process, including all steps (i.e., unit operations),
1218 critical and other process parameters, and IPCs along with their control ranges/acceptance
1219 criteria that are intended to ensure that a drug substance of appropriate quality is consistently
1220 produced.

1221 *3.2.DS.M.2 Development of manufacturing process and process controls*

1222 This section should include process development information and data that support and justify
1223 the process parameters and material attributes necessary to ensure drug substance quality. In
1224 addition, supporting information and data should be included to identify and confirm the
1225 functional relationships of material attributes and process parameters to drug substance CQAs.
1226 If applicable, supporting information and data for the basis for the design space, including risk
1227 analyses studies linking the manufacturing process to drug substance quality may be included
1228 (ICH Q11).

1229 Studies and data of processes models should be included in this section.

1230 Additional information for equipment may be provided in this section.

1231 *3.2.DS.M.3 Extractable and leachable studies*

1232 Extractables and leachables studies for equipment should be provided in this section, where
1233 relevant.

1234 *3.2.DS.M.4 Viral clearance studies*

1235 This section may include information on viral clearance studies.

1236 *3.2.DS.M.5 Changes during development*

1237 Relevant data from comparability studies for drug substance manufacturing development and
1238 the drug substance proposed commercial manufacturing process should be provided.

1239 *3.2.DS.M.6 Comparability for multiple manufacturing sites*

1240 In the case of more than one manufacturing site/process, comparative studies should be
1241 provided.

1242 *3.2.DS.M.7 Process validation or evaluation studies*

1243 This section should include relevant data or studies for process evaluation/validation for
1244 biologics and aseptic processing/sterilisation for chemical entities demonstrating that the
1245 manufacturing process (including any reprocessing) is suitable for its intended purpose and to
1246 substantiate selection of process parameters and IPCs.

1247 **3.2.DS.C Control**

1248 *(Drug Substance Name) [Manufacturer]*

1249 *3.2.DS.C.1 Batch analysis*

1250 This section should include the results of batch analysis or CoAs for relevant batches (for
1251 example stability, nonclinical, and clinical).

1252 *3.2.DS.C.2 Justification of specifications*

1253 Any relevant supportive information and studies/data justifying specification(s) may be
1254 provided here.

1255 **3.2.DS.S Storage**

1256 *(Drug Substance Name) [Manufacturer]*

1257 *3.2.DS.S.1 Container closure system*

1258 Relevant documents for the container closure system which may include extractables and
1259 leachables data/studies should be provided, where appropriate, as well as data from studies
1260 conducted to select and demonstrate the suitability of the container closure systems.

1261 Relevant batch analysis or CoA(s) for container closure system(s) should be provided, as
1262 appropriate.

1263 *3.2.DS.S.2 Stability, storage conditions, and retest period/shelf life*

1264 This section should include relevant information/data in support of justifying storage
1265 conditions and retest period or shelf life of the drug substance. If applicable, relevant
1266 information/data in support of handling and shipping of the drug substance should be provided.

1267 **3.2.SI Substance Intermediates, if Applicable**

1268 *(Substance Intermediate Name) [Manufacturer] [Drug Substance Name]*

1269 This section should include a cross-reference to information in 3.2.DS.M highlighting the steps
1270 that produce substance intermediates.

1271 **3.2.SI.D Description**

1272 *(Substance Intermediate Name) [Manufacturer] [Drug Substance Name]*

1273 If applicable, information on the description of the substance intermediate should be included.

1274 **3.2.SI.M Manufacture**

1275 *(Substance Intermediate Name) [Manufacturer] [Drug Substance Name]*

1276 If applicable, this section may include supportive studies of the manufacture of substance
1277 intermediate. In this case, the applicant should follow all recommendations stated under
1278 3.2.DS.M.

1279 **3.2.SI.C Control**

1280 *(Substance Intermediate Name) [Manufacturer] [Drug Substance Name]*

1281 Batch analysis results should be provided to support the specifications of the substance
1282 intermediates, as appropriate.

1283 **3.2.SI.S Storage**

1284 *(Substance Intermediate Name) [Manufacturer] [Drug Substance Name]*

1285 **3.2.SI.S.1 Container closure system**

1286 Data from studies conducted to select and demonstrate the suitability of the container closure
1287 system and extractables and leachables data/studies should be included, where relevant.
1288 Relevant batch analysis or CoA(s) for container closure system(s) should be provided, as
1289 appropriate.

1290 **3.2.SI.S.2 Stability, storage conditions, and retest period/shelf life**

1291 If applicable, this section should include stability data supporting the storage conditions and
1292 the proposed retest period/shelf life, and shipping conditions of the substance intermediates
1293 (ICH Q1/Q5C).

1294 **3.2.SM Starting/Source Materials**

1295 *(Starting Material Name) [Drug Substance Name]*

1296 **3.2.SM.D Description**

1297 *(Starting Material Name) [Drug Substance Name]*

1298 Additional information on the description of starting/source materials may be provided, as
1299 appropriate.

1300 **3.2.SM.M Manufacture**

1301 *(Starting Material Name) [Drug Substance Name]*

1302 Additional information on manufacture of starting/source materials may be provided, as
1303 appropriate.

1304 **3.2.SM.C Control**

1305 *(Starting Material Name) [Drug Substance Name]*

1306 Where appropriate, this section should include the batch analysis data or CoAs. For biological
1307 starting materials, additional characterisation and adventitious agent control information may
1308 be provided (ICH Q5A, Q5B, Q5D, Q11). The applicant should discuss control of adventitious
1309 agents in 2.3.4.IN.2.2, if applicable (ICH Q5A).

1310 **3.2.SM.S Storage**

1311 *(Starting Material Name) [Drug Substance Name]*

1312 For biological starting materials, additional information on the shipping/stability of the
1313 starting/source material may be provided.

1314 **3.2.RM Raw Materials**

1315 (Raw Material Name) [Drug Substance Name] [Manufacturer] [Intermediate Substance

1316 Manufacturer]

1317 **3.2.RM.D Description**

1318 (Raw Material Name) [Drug Substance Name] [Manufacturer] [Intermediate Substance

1319 Manufacturer]

1320 This section may include additional information on the description of the raw material.

1321 **3.2.RM.M Manufacture**

1322 (Raw Material Name) [Drug Substance Name] [Manufacturer] [Intermediate Substance

1323 Manufacturer]

1324 Additional manufacturing information (e.g., information on manufacture relevant to

1325 adventitious agent control for biological raw materials) may be provided (ICH Q5A).

1326 **3.2.RM.C Control**

1327 (Raw Material Name) [Drug Substance Name] [Manufacturer] [Intermediate Substance

1328 Manufacturer]

1329 If applicable, this section should include batch analysis data or CoA. For biological raw

1330 materials, additional information regarding adventitious agent control may be provided. The

1331 applicant should discuss control of adventitious agents in 2.3.4.IN.2.2, if applicable (ICH

1332 Q5A).

1333 **3.2.RM.S Storage**

1334 (Raw Material Name) [Drug Substance Name] [Manufacturer] [Intermediate Substance

1335 Manufacturer]

1336 For biological raw materials, this section may include supportive stability information/data.

1337 **3.2.EX Excipients**

1338 (Excipient Name) [Drug Product Name] [Manufacturer]

1339 Where appropriate (e.g., for novel excipients and adjuvants), applicable supportive data

1340 regarding description, manufacture, control, and storage may be provided in respective 3.2.EX

1341 sections.

1342 For compendial excipients, these sections will typically be limited to information that justifies

1343 the adequacy of the proposed excipient specifications (e.g., through batch analysis data).

1344 **3.2.EX.D Description**

1345 (Excipient Name) [Drug Product Name] [Manufacturer]

1346 Supportive information/data may be provided on the description, as appropriate.

1347 **3.2.EX.M Manufacture**

1348 (Excipient Name) [Drug Product Name] [Manufacturer]

1349 This section may include information/data on the manufacturing process and process control,

1350 as appropriate.

1351 **3.2.EX.C Control**

1352 (Excipient Name) [Drug Product Name] [Manufacturer]

1353 Batch analysis data may be provided, as appropriate. For biological excipients, additional
1354 information about control of adventitious agents, may be provided, as appropriate (ICH Q5A).

1355 **3.2.EX.S Storage**

1356 *(Excipient Name) [Drug Product Name] [Manufacturer]*

1357 Information/data in support of the claimed storage conditions and retest period/shelf life may
1358 be provided, as appropriate.

1359 **3.2.RS Reference Standards and/or Materials**

1360 *(Reference Standard Name) [Manufacturer] [Drug Substance Name] [Drug Product Name]*

1361 **3.2.RS.D Description**

1362 *(Reference Standard Name) [Manufacturer] [Drug Substance Name] [Drug Product Name]*

1363 This section may include additional information on the description of reference standards
1364 and/or materials.

1365 **3.2.RS.M Manufacture**

1366 *(Reference Standard Name) [Manufacturer] [Drug Substance Name] [Drug Product Name]*

1367 Additional information on the manufacture of in-house reference materials may be provided.

1368 **3.2.RS.C Control**

1369 *(Reference Standard Name) [Manufacturer] [Drug Substance Name] [Drug Product Name]*

1370 For in-house reference materials, batch analysis data should be provided. For biological in-
1371 house reference materials, additional supportive information on characterisation, and
1372 calibration or qualification may be included.

1373 **3.2.RS.S Storage**

1374 *(Reference Standard Name) [Manufacturer] [Drug Substance Name] [Drug Product Name]*

1375 For biological in-house reference materials, stability information/data to support the claimed
1376 use period and storage conditions may be provided.

1377 **3.2.IM Impurities**

1378 **3.2.IM.D Description**

1379 For impurities (chemical impurities, degradants, product- and process-related impurities)
1380 reported in the specifications of drug substance and/or drug product, this section should include
1381 basic information on the impurity such as nomenclature, structural formula, and type/origin.
1382 Information supporting the identification, characterisation, verification, or qualification of the
1383 impurity may also be provided, when appropriate (ICH Q3A, Q3B, Q3C, Q3D, Q3E,
1384 Q6A/Q6B, M7).

1385 For impurities not reported in the specifications, the same basic information may be provided,
1386 as appropriate.

1387 **3.2.IM.M Manufacture**

1388 Not applicable.

1389 **3.2.IM.C Control**

1390 Not applicable.

1391 **3.2.IM.S Storage**
1392 Not applicable.

1393 **3.2.DP Drug Products**
1394 *(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]*

1395 **3.2.DP.D Description**
1396 *(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]*

1397 **3.2.DP.D.1 Components of the drug product**

1398 This section should include information from experimental designs used in identifying critical
1399 or interacting variables that might be important to ensure the quality of the drug product.
1400 Studies that demonstrate the compatibility of drug substance(s) and excipients with each other
1401 and with integral devices, along with information supporting introduction of a device, may also
1402 be included.

1403 **3.2.DP.D.2 Formulation development**

1404 This section should include information and results of the studies and/or published literature
1405 that were used to support the proposed dosage form, formulation development, and to justify
1406 the proposed excipients ranges. For complex dosage forms, additional details or diagrams may
1407 be provided to enhance understanding of the formulation.

1408 **3.2.DP.D.3 Comparability during formulation and product development**

1409 Information on comparative *in vitro* studies (e.g., dissolution) may be included, as appropriate.

1410 Information supporting changes in the device during product development may also be
1411 included.

1412 **3.2.DP.D.4 Physicochemical and biological properties of drug product**

1413 Any supportive information may be provided.

1414 **3.2.DP.D.5 Microbiological attributes**

1415 Any supportive information may be provided.

1416 **3.2.DP.M Manufacture**
1417 *(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]*

1418 **3.2.DP.M.1 Description of manufacturing process**

1419 In support of information provided in 2.3.3, the applicant should include a suitably detailed
1420 description of the commercial manufacturing process including all steps (i.e., unit operations),
1421 critical and other process parameters and IPCs with their control ranges/acceptance criteria that
1422 are intended to ensure that a drug product of appropriate quality is consistently produced.

1423 **3.2.DP.M.2 Development of manufacturing process and process controls**

1424 This section should include data and results from specific development studies and/or
1425 published literature that support the manufacturing process development. Novel processes or
1426 technologies and packaging operations should be described.

1427 Information from process and product monitoring conducted throughout development that is
 1428 used to justify and establish the control strategy for manufacturing should be provided.
 1429 Additionally, studies and experiments that support manufacturing process development and
 1430 monitoring programs, including the risk assessment studies may be provided (ICH Q8, Q9).

1431 This section may include information that provides the basis for the design space(s). This may
 1432 include risk analyses studies and functional relationships linking material attributes and process
 1433 parameters to product CQAs, and risk analyses studies linking the design of the manufacturing
 1434 process to product quality.

1435 Additional information about equipment may be provided in this section.

1436 Studies and data of processes models should be included in this section.

1437 *3.2.DP.M.3 Extractable and leachable studies*

1438 Extractables and leachables studies for equipment should be provided in this section, where
 1439 relevant.

1440 *3.2.DP.M.4 Changes during manufacturing process development*

1441 This section should include comparative studies of significant differences between the
 1442 manufacturing processes used to produce batches for registration/pivotal clinical trials (e.g.,
 1443 safety, efficacy, bioavailability, bioequivalence) or primary stability studies and the proposed
 1444 commercial processes, if applicable.

1445 *3.2.DP.M.5 Comparability for multiple manufacturing sites*

1446 In the case of more than one proposed commercial manufacturing site, comparative information
 1447 should be provided.

1448 *3.2.DP.M.6 Process validation or evaluation studies*

1449 Relevant documentation and results of the process validation and/or evaluation should be
 1450 provided, as appropriate. If applicable, this section should include any studies that support
 1451 proposals for material reprocessing, including studies that demonstrate consistency between
 1452 reprocessed lots and normal production lots.

1453 **3.2.DP.C Control**

1454 *(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]*

1455 *3.2.DP.C.1 Batch analysis*

1456 This section should include the results of batch analysis or CoAs for relevant batches (e.g.,
 1457 stability, nonclinical, and clinical).

1458 *3.2.DP.C.2 Justification of specifications*

1459 Any additional information justifying specification(s) may be provided.

1460 **3.2.DP.S Storage**

1461 *(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]*

1462 **3.2.DP.S.1 Container closure system**

1463 Information about container closure system should be provided which may include extractables
1464 and leachables studies, where relevant, as well as results from studies conducted to select and
1465 demonstrate the suitability of the container closure system. Relevant results of batch analysis
1466 or CoA(s) for container closure system(s) should be provided, as appropriate.

1467 **3.2.DP.S.2 Stability, storage conditions, and shelf life**

1468 This section should include relevant stability results to support storage conditions, shelf life,
1469 and/or holding time for each of the proposed container closure system(s).

1470 Relevant studies/results in support of handling and shipping of the bulk product and drug
1471 product may be provided.

1472 Additional information may be provided to support in-use storage conditions and in-use period
1473 for drug product.

1474 **3.2.PI Product Intermediates, if Applicable**

1475 *(Product Intermediate Name) [Manufacturer] [Drug Product Name]*

1476 **3.2.PI.D Description**

1477 *(Product Intermediate Name) [Manufacturer] [Drug Product Name]*

1478 This section may include data and information that support the composition and development
1479 of the product intermediate.

1480 **3.2.PI.M Manufacture**

1481 *(Product Intermediate Name) [Manufacturer] [Drug Product Name]*

1482 Supportive studies of the manufacture of product intermediate may be included, in accordance
1483 with recommendations stated under 3.2.DP.M.

1484 **3.2.PI.C Control**

1485 *(Product Intermediate Name) [Manufacturer] [Drug Product Name]*

1486 This section should include the results of batch analysis or CoAs to support the specifications
1487 for product intermediate, as appropriate.

1488 **3.2.PI.S Storage**

1489 *(Product Intermediate Name) [Manufacturer] [Drug Product Name]*

1490 **3.2.PI.S.1 Container Closure System**

1491 Information for container closure system should be provided which may include results of
1492 extractables and leachables studies, where relevant, as well as results from studies conducted
1493 to select and demonstrate the suitability of the container closure system. Relevant results of
1494 batch analysis or CoA(s) for container closure system(s) should be provided, as appropriate.

1495 **3.2.PI.S.2 Stability, storage conditions, holding time, and shelf life**

1496 This section should include relevant stability results in support of justifying storage conditions,
1497 holding time/shelf life of product intermediate(s).

1498 Relevant studies/results that support the proposed handling and shipping conditions for the

1499 product intermediate may be provided.

1500 **3.2.MD Medical Devices, if Applicable**

1501 *(Medical Device Name)*

1502 **3.2.MD.D Description**

1503 *(Medical Device Name) [Manufacturer]*

1504 If applicable, this section should include detailed information on the device. This may include

1505 a comprehensive description of the device and its components.

1506 **3.2.MD.M Manufacture**

1507 *(Medical Device Name) [Manufacturer]*

1508 If applicable, detailed information relating to the manufacture of the device should be provided.

1509 This may include a detailed description of the manufacturing process, information related to

1510 the manufacturing process development and commercial manufacturing process, including the

1511 sterilisation step (if applicable), and results of the process validation for critical steps in the

1512 device manufacturing process.

1513 **3.2.MD.C Control**

1514 *(Medical Device Name) [Manufacturer]*

1515 If applicable, this section should include detailed information relating to the control of the

1516 device. This may include information related to the control strategy and/or batch analysis data.

1517 If applicable, validation testing data that confirms that the device meets specified requirements

1518 may be submitted.

1519 **3.2.MD.S Storage**

1520 *(Medical Device Name) [Manufacturer]*

1521 If applicable, this section should include detailed information relating to the storage of the

1522 device before its integration in the medicinal product or for co-packaged device throughout the

1523 medicinal product retest period/shelf life.

1524 **3.2.PM Packaged Medicinal Products for multiconstituent products, if Applicable**

1525 *(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]*

1526 **3.2.PM.D Description**

1527 *(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]*

1528 This section should include information supporting introduction of a device or changes in the

1529 device during medicinal product development may also be provided.

1530 **3.2.PM.M Manufacture**

1531 *(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]*

1532 If the packaging process directly affects product quality, information regarding the process for

1533 packaging of the additionally packaged constituents into the final container should be provided,

1534 as appropriate.

1535 **3.2.PM.C Control**

1536 *(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]*

1537 This section may include analytical results and information for the proposed packaged

1538 medicinal product control strategy.

1539 **3.2.PM.S Storage**

1540 *(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]*

1541 **3.2.PM.S.1 Container closure system**

1542 If functional secondary packaging material is applied to the packaged medicinal product,
 1543 supportive information should be provided.

1544 **3.2.PM.S.2 Stability, storage conditions and shelf life**

1545 This section may include relevant information to support justification of in-use storage
 1546 conditions and in-use period, shipping conditions, as well as storage conditions and shelf life
 1547 of the packaged medicinal product.

1548 **3.2.PH Pharmaceutical Product after transformation, if Applicable**

1549 *(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]*

1550 **3.2.PH.D Description**

1551 *(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]*

1552 Supporting information should be provided, including compatibility tests. Information
 1553 supporting introduction of a device or changes in the device during medicinal product
 1554 development may also be included.

1555 **3.2.PH.M Manufacture**

1556 *(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]*

1557 Not applicable.

1558 **3.2.PH.C Control**

1559 *(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]*

1560 This section should include information to ensure product quality during the intended in-use
 1561 period.

1562 **3.2.PH.S Storage**

1563 *(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]*

1564 **3.2.PH.S.1 Stability, storage conditions, and shelf life**

1565 Relevant information to support justification of in-use storage conditions and in-use period of
 1566 the pharmaceutical product after transformation should be provided.

1567 **3.2.AP Analytical Procedures**

1568 *(Analytical Procedure Name or code) [Purpose] [Material Type]*

1569 This section may include all non-compendial analytical procedures, that are used throughout
 1570 the application, not only the procedures used in support of the control strategy. This section
 1571 may also include analytical procedures including dissolution methods that are used throughout
 1572 the development and comparative studies, but not directly used in the control strategy.

1573 **3.2.AP.1 Analytical Procedure Description**

1574 For analytical procedures already described under 2.3.3.AP, a more detailed description may

1575 be included in this section.

1576 Analytical procedures not described under 2.3.3.AP, and that are referenced in the dossier,
1577 should be presented here. The level of detail should be appropriate for the intended use.

1578 **3.2.AP.2 Analytical Procedure Validation/Qualification**

1579 Where validation is recommended according to ICH Q2, this section should include detailed
1580 data. This may also include verification or method transfer data, where appropriate.
1581 Information on analytical procedures requiring ongoing monitoring and/or periodic
1582 (re)calibration (e.g., model for multivariate analytical procedures) should also be provided in
1583 this section.

1584 **3.2.AP.3 Analytical Procedure Development**

1585 When development information is recommended, related data and information should be
1586 included in this section (ICH Q14 or applicable guidelines).

1587 **3.2.FA Facilities**

1588 *[Manufacturer]*

1589 The applicant should adhere to regional guidelines for their specific submission and product.
1590 For biologics, this section should include the facilities and equipment information listed below.
1591 Regulatory authorities may have different pathways for facility information gathering, such a
1592 Site Master File or GMP certificate from the inspectorate and therefore, may not need the
1593 facility information listed here; whereas other authorities may require additional or less
1594 information than what is listed below.

1595 1. A diagram of the manufacturing facility including:

- 1596 • the manufacturing activities taking place in each room;
- 1597 • the manufacturing flow (including movement of materials, personnel, waste, and
1598 intermediate(s)) in and out of the manufacturing areas;
- 1599 • the classification for each room.

1600 2. Information on the type/classes (e.g., antibody, cytokine, insulin, high-potency drugs) of
1601 all developmental or approved products manufactured or manipulated in the same areas as
1602 the applicant's product, along with the cell line used for each product (e.g., *E. coli*, CHO).

1603 3. A summary description of product-contact equipment, and its use (i.e., dedicated or shared
1604 use, manufacturing step(s) where it is used).

1605 4. The cleaning strategy, e.g., shared use equipment, change-over process, demonstration of
1606 adequacy of cleaning.

1607 5. A summary of the environmental monitoring program in aseptic manufacturing area.

1608 6. Information on sterilisation of specified equipment and product components.

1609 In addition, the applicant may be able to refer to a previously submitted application for the
1610 same facility.

1611	ABBREVIATIONS
1612	AP - Analytical Procedure
1613	ATMP - Advanced Therapy Medicinal Products
1614	CoA - Certificate of AnalysisCQA - Critical Quality Attributes
1615	CQI - Core Quality Information
1616	DMCS - Description, Manufacture, Control, and Storage
1617	DP - Drug Product
1618	DS - Drug Substance
1619	ECs - Established Conditions
1620	EX - Excipient
1621	FA – Facilities
1622	IN - Integrated Development and Justification
1623	IPC - In Process Control
1624	MD - Medical Device
1625	OCS - Overall Control Strategy
1626	PM - Packaged Medicinal Product
1627	PACMP - Post Approval Change Management Protocol
1628	PH – Pharmaceutical Product
1629	PLCM - Product Lifecycle Management
1630	PQBR - Product Quality Benefit Risk
1631	PI - (Drug) Product Intermediate
1632	QTPP - Quality Target Product Profile
1633	RM - Raw Material
1634	RS - Reference Standard
1635	RTRT - Real Time Release Testing

1636 SI - (Drug) Substance Intermediate

1637 SM - Starting/Source Material

Term(s)	Definition	Reference/Related Terms
Analytical procedure	The analytical procedure refers to the way of performing the analysis. It should describe in detail the steps necessary to perform each analytical test. This may include but is not limited to: the sample, the reference standard and the reagents preparations, use of the apparatus, generation of the calibration curve, use of the formulae for the calculation, etc.	ICH Q2
Bioinformatics	Bioinformatics is an interdisciplinary field that combines biology, computer science, mathematics, and statistics to analyse and interpret biological data. It involves the use of computational tools and techniques to manage, process, and understand complex biological information, particularly large datasets generated by experiments such as DNA sequencing, protein structure analysis, and gene expression studies.	
Bulk Material (Biologics)	The material which is subsequently formulated with excipients to produce the drug product. It can be composed of the desired product, product-related substances, and product- and process-related impurities. It may also contain excipients including other components such as buffers.	ICH Q6B
Bulk Product	Bulk finished dosage form, that has completed all processing stages before immediate packaging <i>Note 1: This includes materials that may be held in potentially large quantities for an extended period of time under controlled and justified conditions (e.g. 10 000 tablets intended for blistering or 100L of solution for injection intended to fill vials)</i> <i>Example: film-coated tablet or solution for injection before immediate packaging</i>	M4Q(R2) adapted from ICH Q6B/Bulk Material
(Chemical) Development Studies	Studies conducted to scale-up, optimise, and validate the manufacturing process for a new drug substance or a drug product.	ICH Q3A/B
Container Closure System	The sum of packaging components that together contain and protect the finished dosage form or any other material. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional	ICH M4Q(R2) adapted from ICH Q1A

Term(s)	Definition	Reference/Related Terms
	protection to the drug product or packaged material.	
Contamination	The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or drug substance during production, sampling, packaging or repackaging, storage or transport.	ICH Q7
Control Strategy	A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.	ICH Q10
Dosage Form	The type of physical manifestation (e.g., tablet, capsule, solution, cream, powder).	ICH M4Q(R2) Adapted from ISO IDMP
Drug Product	The Finished Dosage Form in the final immediate packaging intended for sale or supply. <i>Note: Some Drug Products do not necessarily include a Drug Substance (e.g. solvent for solution for injection in vial)</i> <i>Note: Label is not included</i> <i>Examples: film-coated tablet in blister or solution for injection in vial, solvent for solution for injection in vial</i>	ICH M4Q(R2)
Drug Release Profile	Speed/rate at which a drug is released.	
Drug Substance	Any substance or mixture of substances intended to be used in the manufacture of a finished dosage form and that, when so used, becomes an active ingredient of that finished dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.	ICH M4Q(R2) Adapted from ICH Q7/ Active Substance/ Active Ingredient
Excipient	–A substance or compound, other than the drug substance and packaging materials,	ICH M4Q(R2)

Term(s)	Definition	Reference/Related Terms
	that is intended or designated to be used in the manufacture of a finished dosage form. <i>Note: Excipients include e.g. fillers, disintegrants, lubricants, colouring matters, antioxidants, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, solubilisers, permeation enhancers, flavouring and aromatic substances, processing aids etc., as well as the constituents of the outer covering of the finished dosage form, e.g. gelatine capsules.</i>	
Finished Dosage Form	Final qualitative and quantitative composition containing one or more ingredients in the specific manufactured dosage form intended to be part of a drug product <i>Note: Some Finished Dosage Form do not necessarily include a Drug Substance (e.g. solvent for solution for injection)</i> <i>Example: film coated tablet or solution for injection with specific qualitative and quantitative composition</i>	ICH M4Q(R2)/ <i>Manufactured Item (ISO IDMP 11615)</i>
Functional secondary packaging material	Secondary packaging material considered critical to ensure the quality of the packaged substance/ product <i>Example: provides additional protection like for moisture sensitive products or serves to deliver the product</i>	ICH M4Q(R2) adapted from ICH
Impurity	(1) Any component of the new drug substance which is not the chemical entity defined as the new drug substance. (2) Any component of the drug product which is not the chemical entity defined as the drug substance or an excipient in the drug product. (3) Any component present in the drug substance or drug product which is not the desired product, a product-related substance, or excipient including buffer components. It may be either process- or product-related.	ICH Q6A/B/ Degradation product
Material	A general term used to denote raw materials, starting materials, substance intermediates, drug substances, excipients, reference standards, product intermediates, finished dosage forms, and packaging and labelling materials.	ICH M4Q(R2) Adapted from ICH Q7
Medicinal Product	Pharmaceutical product or combination of pharmaceutical products that can be administered to human beings or animals for treating or preventing disease, with the aim of making a medical diagnosis or to restore, correct or modify physiological functions	ISO IDMP 11615

Term(s)	Definition	Reference/Related Terms
	<i>Note 1: A medicinal product may contain in the packaging one or more finished dosage form(s), and one or more pharmaceutical products.</i> <i>Note 2: In certain regions, a medicinal product is defined as any substance or combination of substances that can be used to make a medical diagnosis.</i>	
Multiconstituent Product(s)	Multiconstituent products consist of two or more constituents that are intended to be used together for a specific therapeutic, diagnostic or preventive purpose, and that are packaged in a container or in a unit as a marketing pack. Multiconstituent products may include one or more drug product constituents, or a combination of these with additional finished dosage forms and/or medical device(s). <i>Examples: a vial containing powder for solution for injection may be packaged with a vial containing the vehicle for preparation of solution for reconstitution, along with two syringes: one for preparation of the solution for injection and the other for administration of the solution for injection</i>	ICH M4Q(R2)
Packaging Material	Any material intended to protect another material during storage and transport.	ICH M4Q(R2) adapted from ICH Q7
Packaged Medicinal Product	Medicinal Product in a container being part of a package, representing the entirety that has been packaged for sale or supply <i>Note: Packaged Medicinal Product may contain Multiconstituent Product</i> <i>Examples: film-coated tablet in blister in carton box or solution for injection in vial in carton box or one vial with powder for solution for injection is packaged with one vial with the vehicle for preparation of solution for reconstitution and with two syringes for preparation of the solution for injection and for administration of the solution for injection in a carton box</i>	ISO IDMP/ Marketing Pack
Pharmaceutical Product	Qualitative and quantitative composition of the product as administered to the patient in line with regulated product information. <i>Note 1: In many instances, the pharmaceutical product is equal to the finished dosage form. However, there are instances where the finished dosage form must undergo a transformation before being administered to the patient (as the pharmaceutical product) and the two are not equal.</i> <i>Examples: film-coated tablet (taken without transformation) or reconstituted solution for injection using one vial with powder for solution for injection is packaged with one vial with the vehicle for preparation of solution for reconstitution.</i>	ISO IDMP

Term(s)	Definition	Reference/Related Terms
(Drug) Product Intermediate	A material that is produced as part of the drug product manufacturing process after the defined drug substance(s) and subject to further processing before the finished dosage form. <i>Note 1: Generally, a product intermediate will have established specifications to determine the successful completion of its manufacture before the continuation of the drug product manufacturing process.</i> <i>Note 2: This includes materials that may be held for an extended period of time under controlled and justified conditions or tested against the established specification immediately prior to further processing.</i> <i>Note 3: A product intermediate may be produced by the final drug product manufacturer or manufactured or sourced via an independent manufacturing process by a different manufacturer</i> <i>Note 4: A product intermediate may not contain the drug substance such as excipient mixtures, granulated excipients, tablet core without drug substance, placebo intermediates.</i>	ICH M4Q(R2) Adapted from ICH Q5C/ Pharmaceutical intermediate
Quality	The suitability of either a drug substance or a drug product for its intended use. This term includes such attributes as identity, strength, and purity. The degree to which a set of inherent properties of a product, system or process fulfils requirements.	ICH Q6A ICH Q9
Raw Material	A general term used to denote reagents, solvents and processing aids intended for use in the production of substance intermediate(s) or drug substance(s) and not being the defined starting material(s).	Adapted from ICH Q7
Reference Standard	Primary - A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be: (1) obtained from an officially recognised source, or (2) prepared by independent synthesis, or (3) obtained from existing production material of high purity, or (4) prepared by further purification of existing production material. Secondary - A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.	ICH Q7/ Reference Standard In-house Primary Reference Material Reference standards and/or material Specified substance ICH Q7/Reference

Term(s)	Definition	Reference/Related Terms
		Standard In-house Working Reference Material Secondary Reference Standard Specified Substance
(Drug) Substance Intermediate	A material that is produced as part of the end-to-end drug substance manufacturing process after the defined starting material(s) and subject to further processing before the drug substance. <i>Note 1: Substance intermediates may or may not be isolated.</i> <i>Note 2: Generally, a substance intermediate will have established specifications or in-process controls to determine the successful completion of its manufacture before the continuation of the drug substance manufacturing process.</i> <i>Note 3: This includes materials that may be held for an extended period of time under controlled and justified conditions or tested against the established specification immediately prior to further processing</i> <i>Note 4: A substance intermediate can be produced in-house by the main drug substance manufacturer or manufactured or sourced via a separate manufacturing process or by a different manufacturer</i> <i>Note 5: In some cases, the active substance might be considered as a substance intermediate of the final drug substance (e.g. diclofenac free base is a substance intermediate of the diclofenac sodium drug substance)</i> <i>Note 6: For very complex end to end biologic drug substance manufacturing processes or cases where the sub-part of the end-to-end drug substance manufacturing process up to a specific substance intermediate is performed by a different manufacturer, the applicant may segregate the manufacture of specific substance intermediates (e.g. viral vectors, ADC linker etc.) from the main drug substance manufacturing process.</i> <i>Note 7: The level of quality information expected for a substance intermediate will depend on its complexity and on the potential impact of the quality of this material to the quality of the final drug substance; with higher level risk materials (e.g. viral vectors, ADC linkers, etc.) requiring a level of information close to a drug substance.</i> <i>Examples: an isolated or non-isolated substance intermediate manufactured as part of the main drug substance manufacturing process, or a chemical or a biological substance manufactured outside of the main drug substance manufacturing process (a linker used in ADC manufacture, a viral vector used in</i>	ICH M4Q(R2) Adapted from ICH Q5C

Term(s)	Definition	Reference/Related Terms
	cell and gene therapy manufacture etc.). Further processing examples: further chemical transformation, further molecular change/modification, purification	
Starting/Source Material	A material from which the drug substance is extracted or used in the production of a drug substance and ultimately incorporated as an element into the structure of the drug substance (directly or via one of its substance intermediate). <i>Note 1: Starting material can be commercially available, produced in-house by the final drug substance manufacturer or externally by one or more different manufacturers under contract or commercial agreement.</i> <i>Note 2: Starting materials are normally of defined chemical properties and structure.</i>	ICH M4Q(R2) Adapted from ICH Q3A(R2)
Specification	A list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug substance and / or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.	ICH Q6A/B
Substance	Matter of defined composition that has discrete existence, whose origin may be biological, mineral or chemical.	ISO IDMP
Transformation	Procedure that is carried out in order to convert a finished dosage form that requires such a modification into a pharmaceutical product, i.e. from its manufactured dosage form to its administrable dosage form <i>Note 1: A transformation is not required when the drug product dosage form is equal to the pharmaceutical product.</i> <i>Note 2: In certain circumstances, the transformation may be used, alone or in combination with one or more other pharmaceutical dosage form attributes, to describe a medicinal product where a pharmaceutical dosage form term cannot be used, for example as part of an adverse event report in which the precise pharmaceutical dosage form is unknown, but the transformation is known.</i>	ICH M4Q(R2) Adapted from ISO IDMP 11615

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Term(s)	Definition	Reference/Related Terms
	<i>Note 3: The transformation should be applied within context of product quality and M4Q (R2) guideline and should not be interpreted in a biological sense, such as genetic cellular alterations or change from normal to malignant cells etc.</i> <i>Examples: Dilution, dissolution, dispersion, suspension, reconstitution.</i>	

1641 **REFERENCES**

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- 1647 ICH Q5A(R2): Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of
1648 Human or Animal Origin
- 1649 ICH Q5B: Quality Of Biotechnological Products: Analysis of the Expression Construct in Cells
1650 Used For Production of R-DNA Derived Protein Products
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1654 Biotechnological/Biological Products
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