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**GUIDELINE ON SUBMISSION OF DOCUMENTATION FOR A  
MULTISOURCE (GENERIC) FINISHED PHARMACEUTICAL  
PRODUCT (FPP): QUALITY PART**

***DRAFT FOR COMMENT***

Please address comments on this proposal, by 30 July 2011. All comments should be sent to Dr M. Stahl, Prequalification Programme, Quality Assurance & Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland, fax: (+41 22) 791 4730 or e-mail: stahlm@who.int.

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SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT  
QAS/10.373:

Drafting of guideline by G. Condran and L. Paleshnuik	7 June 2010
Discussion and review of comments within the Prequalification Programme assessment group	June 2010
Consolidation of comments and review	July 2010
Circulation of revised draft for comments	August 2010
Presentation to the forty-fifth WHO Expert Committee on Specifications for Pharmaceutical Preparations	18-22 October 2010
Review of text in connection of the new draft working document on Points to Consider for the development of Multisource (generics) medicines	February-March 2011
Discussion during the informal consultation on development of paediatric and generic medicines	4-6 May 2011
Mailing of revised draft for comments	June 2011
Collation of comments received	August 2011
Review of comments by a small subgroup	September 2011
Presentation to the 46 <sup>th</sup> WHO Expert Committee on Specifications for Pharmaceutical Preparations	10-14 October 2011
Any further action as required	

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During the development of this guideline, 26 manufacturers, who actively participate in the Prequalification Programme, have been contributing and were involved in the consultation process which led to the first draft of this document. In addition, the draft was made available for comments on the WHO web site, both under the Expert Committee meeting documentation, as well as the Prequalification Programme web site. The text was also presented during workshops organized by the Prequalification Programme. The concept has been implemented since September 2010 in submission to the prequalification process. To date, the feedback has been positive.

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Revised draft for comment

86 **1. INTRODUCTION**

87

88 1.1 Background

89

90 WHO Technical Report Series, No. 953, Annex 3 (2009) entitled *Procedure for*  
91 *prequalification of pharmaceutical products* (TRS No. 953) outlines the procedure and  
92 considerations for the process undertaken by WHO in providing United Nations agencies with  
93 advice on the acceptability in principle of pharmaceutical products for procurement by such  
94 agencies. WHO Technical Report Series, No. 953 states:

95 *"This activity of WHO aims to facilitate access to priority essential medicines that*  
96 *meet WHO-recommended norms and standards of acceptable quality."*

97 As mentioned in WHO Technical Report Series, No. 953, in submitting an expression of  
98 interest (EOI) for product evaluation, the applicant should send to the WHO focal point  
99 (together with the other data requirements) a *product dossier* (PD), in the format specified in  
100 the WHO guidance documents on submitting product data and information.

101

102 Through the International Conference on Harmonisation (ICH) process, considerable  
103 harmonization has been achieved on the organization for the *Quality Module* of the  
104 registration documents with the issuance of the Common Technical Document (CTD) -  
105 Quality (ICH M4Q) guideline. This recommended format in the M4Q guideline for the  
106 quality information of registration applications has become widely accepted by regulatory  
107 authorities both within and beyond the ICH Regions.

108

109 This document, *Guideline on submission of documentation for a multisource (generic)*  
110 *finished pharmaceutical product (FPP): quality part*, provides recommendations on the  
111 quality information for active pharmaceutical ingredients (APIs) and finished pharmaceutical  
112 products (FPPs) that should be submitted to WHO to support PDs.

113

114 Alternate approaches to the principles and practices described in this document may be  
115 acceptable provided they are supported by adequate scientific justification. It is also  
116 important to note that the Prequalification Programme may request information or material, or  
117 define conditions not specifically described in this guidance, in order to adequately assess the  
118 quality of a pharmaceutical product.

119

120 1.2 Objectives

121

122 This guideline is intended to:

- 123 • assist applicants on the preparation of the *Quality Module* of PDs for multisource  
124 products by providing clear general guidance on the format of these dossiers;
- 125 • fully adopt the modular format of the *Common Technical Document - Quality (M4Q)*  
126 as developed by ICH; and
- 127 • provide guidance on the technical and other general data requirements.

128

129 These measures are intended to promote effective and efficient processes for the development  
130 of these PDs by applicants and the subsequent assessment procedures by WHO.

131

132 1.3 Scope

133

134 This guideline applies to PDs for multisource pharmaceutical products containing existing  
135 APIs of synthetic or semisynthetic origin. For the purposes of this guideline, an existing API  
136 is one that has been previously authorized through a finished product by a stringent regulatory  
137 authority.<sup>1</sup> APIs from fermentation, biological, biotechnological or herbal origin are covered  
138 by other guidelines.

139

140 1.4 General principles

141

142 To facilitate the preparation of the PD, this guideline is organized in accordance with the  
143 structure of the *Common Technical Document – Quality (M4Q)* guideline, as developed by  
144 ICH.

145

146 The text of the M4Q (CTD-Q) guideline has been restated in this guideline in **bold text**,  
147 *verbatim*, with minor modifications to accommodate WHO terminology and include certain  
148 text that would be appropriate for multisource pharmaceutical products, notably:

149

- “Drug substance” is replaced with “active pharmaceutical ingredient” or “API”;
- “Drug product” is replaced with “finished pharmaceutical product” or “FPP”;
- “application” is replaced with “product dossier” or “PD”;
- “combination product” is replaced with “fixed-dose combination” or “FDC”;
- “clinical batches” is replaced with “comparative bioavailability or biowaiver batches”.

154

155 Following the **bold** text of the M4Q (CTD-Q) guideline, additional guidance by WHO is  
156 provided in plain text to easily distinguish from the ICH text and is included to provide  
157 further clarity on WHO’s expectations for the content of PDs. This approach is intended to  
158 facilitate the identification and origin of the text in the guideline (i.e. from ICH or WHO).

159

160 The content of this guideline should be read in conjunction with relevant information  
161 described in other existing WHO or ICH reference documents and guidelines. The quality of  
162 existing APIs and corresponding multisource products should not be inferior to new APIs and  
163 innovator (comparator) FPPs. Therefore, the principles of the ICH guidelines that are  
164 referenced throughout this and other WHO guidelines may also equally apply to existing APIs  
165 and multisource products.

166

167 Scientific literature may be appropriate to fulfil the requirements for some of the information  
168 or parameters outlined in this guideline (e.g. qualification of specified identified impurities).  
169 Furthermore, the requirements outlined in certain sections may not be applicable for the  
170 proposed API or FPP. In these situations, a summary and the full reference to the scientific  
171 literature should be provided or the non-applicability of the requested information should be  
172 clearly indicated as such with an accompanying explanatory note.

---

<sup>1</sup> *Stringent regulatory authority (SRA): a regulatory authority which is:  
a member of the International Conference on Harmonisation (ICH) (as specified on www.ich.org);  
or  
an ICH observer, being the European Free Trade Association (EFTA), as represented by Swiss  
Medic, and Health Canada (as may be updated from time to  
time); or  
a regulatory authority associated with an ICH member through a legally-binding, mutual  
recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be  
updated from time to time).*

173

174 1.5 Guidance on format

175

176 The recommendations outlined in the WHO general filing guideline *Guideline on submission*  
177 *of documentation for a multisource (generic) finished pharmaceutical product (FPP):*  
178 *preparation of product dossiers (PDs) in common technical document (CTD) format* should  
179 be followed for the format and presentation of the PD.

180

181 There may be a number of instances where repeated sections can be considered appropriate.  
182 Whenever a section is repeated, it should be made clear what the section refers to by creating  
183 a distinguishing title in parentheses following the M4Q (CTD-Q) guideline heading, e.g. 3.2.S  
184 Drug substance (or API) (name, Manufacturer A).

185

186 Following are recommendations for the presentation of the information in the *Quality Module*  
187 for different scenarios that may be encountered:

188 • the *Open part* (nonproprietary information) of each APIMF should always be included  
189 *in its entirety* in the PD, as an annex to 3.2.S;

190 • for an FPP containing more than one API: one complete “3.2.S” section should be  
191 provided for one API, *followed by* other complete “3.2.S” sections for each other API;

192 • for an API from multiple manufacturers: one complete “3.2.S” section should be  
193 provided for the API from one manufacturer, *followed by* other complete “3.2.S”  
194 sections for each other API manufacturer;

195 • for an FPP with multiple strengths (e.g. 10, 50, 100 mg): one complete “3.2.P” section  
196 should be provided with the information for the different strengths provided *within* the  
197 subsections. One complete copy of the PD should be provided for each FPP strength;

198 • for an FPP with multiple container-closure systems (e.g. bottles and unit dose blisters):  
199 one complete “3.2.P” section should be provided with the information for the different  
200 presentations provided *within* the subsections;

201 • for multiple FPPs (e.g. tablets and a parenteral product): a separate dossier is required  
202 for each FPP;

203 • for an FPP supplied with reconstitution diluent(s), one complete “3.2.P” section  
204 should be provided for the FPP, *followed by* the information on the diluent(s) in a  
205 separate part “3.2.P”, as appropriate; and

206 • for a coblistered FPP, one complete “3.2.P” section should be provided for each  
207 product.

208

## 209 2. GLOSSARY

210

211 The definitions provided below apply to the words and phrases used in these guidelines.  
212 Although an effort has been made to use standard definitions as far as possible, they may  
213 have different meanings in other contexts and documents. The following definitions are  
214 provided to facilitate interpretation of the guidelines.

215

216 *active pharmaceutical ingredient (API)*

217 Any substance or combination of substances used in a finished pharmaceutical product (FPP),  
218 intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis,  
219 cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring,

220 correcting or modifying physiological functions in human beings (reference: WHO Technical  
221 Report Series, No. 953, Annex 3, 2009).

222

223 *API starting material*

224 A raw material, intermediate, or an API that is used in the production of an API and that is  
225 incorporated as a significant structural fragment into the structure of the API. An API starting  
226 material can be an article of commerce, a material purchased from one or more suppliers  
227 under contract or commercial agreement, or produced in-house (reference: ICH Q7). See also  
228 *starting materials for synthesis*.

229

230 *applicant*

231 The person or entity who, by the deadline mentioned in the invitation, submits an expression  
232 of interest (EOI) to participate in this procedure in respect of the product(s) listed in the  
233 invitation, together with the required documentation on such product(s) (reference: WHO  
234 Technical Report Series, No. 953, Annex 3, 2009).

235

236 *BCS highly soluble*

237 An API for which the highest dose recommended by WHO (if the API appears on the *WHO*  
238 *Model List of Essential Medicines*) or highest dose strength available on the market as an oral  
239 solid dosage form (if the API does not appear on the *WHO Model List of Essential*  
240 *Medicines*) is soluble in 250 ml or less of aqueous media over the pH range of 1.2–6.8 at 37  
241 °C (reference: WHO Technical Report Series, No. 937, Annex 7, 2006).

242

243 *commitment batches*

244 Production batches of an API or FPP for which the stability studies are initiated or completed  
245 post-approval through a commitment made in a regulatory application (reference: WHO  
246 Technical Report Series, No. 953, Annex 2, 2009).

247

248 *comparator product*

249 A pharmaceutical product with which the generic product is intended to be interchangeable in  
250 clinical practice. The comparator product will normally be the innovator product for which  
251 efficacy, safety and quality have been established (reference: WHO Technical Report Series,  
252 No. 937, Annex 7, 2006). For the Prequalification Programme, the selection of the  
253 comparator product is based on the information presented under Guidance on Bioequivalence  
254 Studies available on the Prequalification web site.

255

256 *established multisource (generic) product*

257 A multisource product that has been marketed by the applicant or manufacturer associated  
258 with the dossier for at least five years and for which at least 10 production batches were  
259 produced over the previous year, or, if less than 10 batches were produced in the previous  
260 year, not less than 25 batches were produced in the previous three years.

261

262 *existing API*

263 An API that is not considered a new active substance, that has been previously authorized  
264 through a finished product by a stringent regulatory authority, but requires the filing of a  
265 WHO dossier. This would include, for example, new PDs and variations to multisource  
266 products.

267

268 *finished pharmaceutical product (FPP)*

269 A finished dosage form of a pharmaceutical product, which has undergone all stages of  
270 manufacture, including packaging in its final container and labelling (reference: WHO  
271 Technical Report Series, No. 953, Annex 3, 2009).

272

273 *innovator pharmaceutical product*

274 Generally the pharmaceutical product that was first authorized for marketing (normally as a  
275 patented product) on the basis of documentation of efficacy, safety and quality (reference:  
276 WHO Technical Report Series, No. 937, Annex 7, 2006).

277

278 *manufacturer*

279 A company that produces, packages, repackages, labels and/or relabels pharmaceutical  
280 products (reference: WHO Technical Report Series, No. 953, Annex 3, 2009).

281

282 *multisource (generic) pharmaceutical products*

283 Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be  
284 therapeutically equivalent. Multisource pharmaceutical products that are therapeutically  
285 equivalent are interchangeable (reference: WHO Technical Report Series, No. 937, Annex 7,  
286 2006).

287

288 *officially recognized pharmacopoeia (or compendium)*

289 Those pharmacopoeias recognized in the WHO Prequalification Programme (i.e. *The*  
290 *International Pharmacopoeia* (Ph.Int.), the European Pharmacopoeia (PhEur), the British  
291 Pharmacopoeia (BP), the Japanese Pharmacopoeia (JP) and the United States Pharmacopoeia  
292 (USP)).

293

294 *ongoing stability study*

295 The study carried out by the manufacturer on production batches according to a  
296 predetermined schedule in order to monitor, confirm and extend the projected re-test period  
297 (or shelf-life) of the API, or confirm or extend the shelf-life of the FPP (reference: WHO  
298 Technical Report Series, No. 953, Annex 2, 2009).

299

300 *pilot-scale batch*

301 A batch of an API or FPP manufactured by a procedure fully representative of and simulating  
302 that to be applied to a full production-scale batch. For example, for solid oral dosage forms, a  
303 pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100 000  
304 tablets or capsules, whichever is the larger; unless otherwise adequately justified (reference:  
305 WHO Technical Report Series, No. 953, Annex 2, 2009).

306

307 *primary batch*

308 A batch of an API or FPP used in a stability study, from which stability data are submitted in  
309 a registration application for the purpose of establishing a re-test period or shelf-life  
310 (reference: WHO Technical Report Series, No. 953, Annex 2, 2009). For the Prequalification  
311 Programme, primary batch requirements are outlined in 3.2.S.7.1 and 3.2.P.8.1 for the API  
312 and FPP, respectively.

313

314 *production batch*

315 A batch of an API or FPP manufactured at production scale by using production equipment in  
316 a production facility as specified in the application (reference: WHO Technical Report Series,  
317 No. 953, Annex 2, 2009).

318

319 *starting materials for synthesis*  
320 Materials that mark the beginning of the manufacturing process as described in an application  
321 or in an APIMF. A starting material for a synthetic API is a chemical compound of defined  
322 molecular structure that contributes to the structure of the API. See also *API starting material*.  
323

### 324 3. QUALITY SUMMARIES

#### 325 3.1 Module 2.3: Quality overall summary – product dossiers (QOS-PD)

326  
327  
328 **The quality overall summary (QOS) is a summary that follows the scope and the outline**  
329 **of the Body of Data in Module 3. The QOS should not include information, data or**  
330 **justification that was not already included in Module 3 or in other parts of the common**  
331 **technical document (CTD).**

332  
333 **The QOS should include sufficient information from each section to provide the quality**  
334 **assessor with an overview of Module 3. The QOS should also emphasize critical key**  
335 **parameters of the product and provide, for instance, justification in cases where**  
336 **guidelines were not followed. The QOS should include a discussion of key issues that**  
337 **integrates information from sections in the Quality Module and supporting information**  
338 **from other Modules (e.g. qualification of impurities via toxicological studies), including**  
339 **cross-referencing to volume and page number in other Modules.**

340  
341 The WHO *quality overall summary – product dossiers (QOS-PD)* template should be  
342 completed for multisource pharmaceutical products containing APIs of synthetic or  
343 semisynthetic origin (see 1.3 Scope for further clarification) and their corresponding FPPs.  
344

345 All sections and fields in the QOS-PD template that would be applicable should be completed.  
346 It is understood that certain sections and fields may not apply and should be indicated as such  
347 by reporting “not applicable” in the appropriate area with an accompanying explanatory note.  
348

349 The use of tables to summarize the information is encouraged, where possible. The tables  
350 included in the template may need to be expanded or duplicated (e.g. for multiple strengths),  
351 as necessary. These tables are included as illustrative examples of how to summarize  
352 information. Other approaches to summarize information can be used if they fulfil the same  
353 purpose.  
354

#### 355 3.2 Module 1.4.2: Quality information summary (QIS)

356  
357 The quality information summary (QIS) template should be completed to provide a *condensed*  
358 *summary* of the *key quality information* for the PD and constitute part of the submission  
359 package. The QIS provides an accurate record of technical data in the PD at the time of  
360 prequalification. The QIS is a condensed version of the QOS-PD and represents the final  
361 agreed upon *key active pharmaceutical ingredient (API) and finished pharmaceutical product*  
362 *(FPP) information* from the PD assessment (inter alia identification of the  
363 manufacturer(s)/site addresses, API/FPP specifications, stability conclusions and relevant  
364 commitments).  
365

366 The QIS template is structured according to the numbering and section headings of the ICH  
367 M4Q (CTD-Q) guideline to permit the rapid assembly of the QIS by copying requisite  
368 information from the corresponding portions of the QOS-PD filed with the PD. It is  
369 acknowledged that the numbering of the sections in the QIS may not be entirely sequential.

370 Those sections not considered necessary to be included in the QIS have been removed (e.g.  
371 2.3.S.5 Reference standards or materials) and the remaining sections have retained their  
372 numbering to be consistent with the original PD.

373  
374 The QIS will serve as an official reference document in the course of good manufacturing  
375 practices (GMP) inspections, variation assessments and requalification assessments as  
376 performed by WHO.

#### 377 378 **4. MODULE 3: QUALITY**

379  
380 4.1 Table of contents of Module 3

381  
382 **A table of contents for the filed product dossier should be provided.**

383  
384 4.2 Body of data

#### 385 386 **3.2.S Drug substance (or active pharmaceutical ingredient (API))**

387  
388 The API information can be submitted to WHO in one of the following three options:

- 389
- 390 • Option 1: Certificate of suitability of the European Pharmacopoeia (CEP); or
  - 391 • Option 2: Active pharmaceutical ingredient master file (APIMF) procedure; or
  - 392 • Option 3: Full details in the PD.
- 393

394 The applicant should clearly indicate at the beginning of the API section (in the PD and in the  
395 QOS-PD) how the information on the API for each API manufacturer is being submitted. The  
396 API information submitted by the applicant/FPP manufacturer should include the following  
397 for each of the options used.

- 398
- 399 • *Option 1: Certificates of Suitability of the European Pharmacopoeia (CEP)*
- 400

401 A complete copy of the CEP (including any annexes) should be provided in *Module 1*.  
402 The declaration of access for the CEP should be duly filled out by the CEP holder on  
403 behalf of the FPP manufacturer or applicant to the Prequalification Programme who  
404 refers to the CEP.

405  
406 In addition, a written commitment should be included that the applicant will inform  
407 WHO in the event that the CEP is withdrawn. It should also be acknowledged by the  
408 applicant that withdrawal of the CEP will require additional consideration of the API  
409 data requirements to support the PD. The written commitment should accompany the  
410 copy of the CEP in *Module 1*.

411  
412 Along with the CEP the applicant should supply the following information in the  
413 dossier, with data summarized in the QOS-PD.

- 414
- 415 ○ *3.2.S.1.3 General properties* – discussions on any additional applicable  
416 physicochemical and other relevant API properties that are not controlled by  
417 the CEP and PhEur monograph, e.g. solubilities and polymorphs as per  
418 guidance in this section.

- 419 ○ 3.2.S.3.1 *Elucidation of structure and other characteristics* – studies to identify  
420 polymorphs (exception: where the CEP specifies a polymorphic form) and  
421 particle size distribution, where applicable, as per guidance in this section.  
422 ○ 3.2.S.4.1 *Specification* – the specifications of the FPP manufacturer including  
423 all tests and limits of the CEP and PhEur monograph and any additional tests  
424 and acceptance criteria that are not controlled in the CEP and PhEur  
425 monograph, such as polymorphs and/or particle size distribution.  
426 ○ 3.2.S.4.2/3.2.S.4.3 *Analytical procedures and validation* – for any tests in  
427 addition to those in the CEP and PhEur monograph.  
428 ○ 3.2.S.4.4 *Batch analysis* – results from two batches of at least pilot scale,  
429 demonstrating compliance with the FPP manufacturer's API specifications.  
430 ○ 3.2.S.5 *Reference standards or materials* – information on the FPP  
431 manufacturer's reference standards.  
432 ○ 3.2.S.6 *Container-closure system* – specifications including descriptions and  
433 identification of primary packaging components.  
434 ○ 3.2.S.7 *Stability* – exception: where the CEP specifies a re-test period that is  
435 the same as or of longer duration than the re-test period proposed by the  
436 applicant.

437  
438 In the case of sterile APIs, data on the sterilization process of the API, including  
439 validation data, should be included in the PD.  
440

441 • *Option 2: Active pharmaceutical ingredient master file (APIMF) procedure*  
442

443 Full details of the chemistry, manufacturing process, quality controls during  
444 manufacturing and process validation for the API may be submitted as an APIMF by  
445 the API manufacturer as outlined in WHO's *Guidelines on active pharmaceutical*  
446 *ingredient master file procedure* (Technical Report Series, No. 948, Annex 4, 2008).  
447

448 In such cases, the *Open part* (nonproprietary information) needs to be included *in its*  
449 *entirety* in the PD as an annex to 3.2.S. In addition, the applicant/FPP manufacturer  
450 should complete the following sections in the PD and QOS-PD *in full* according to the  
451 guidance provided unless otherwise indicated in the respective sections:  
452

453 *General information* S.1.1 through S.1.3

454 *Manufacture* S.2

455 *Manufacturer(s)* S.2.1

456 *Description of manufacturing process and process controls* S.2.2

457 *Controls of critical steps and intermediates* S.2.4

458 *Elucidation of structure and other characteristics* S.3.1

459 *Impurities* S.3.2

460 *Control of the API* S.4.1 through S.4.5

461 *Reference standards or materials* S.5

462 *Container-closure system* S.6

463 *Stability* S.7.1 through S.7.3  
464

465 It is the responsibility of the applicant to ensure that the complete APIMF (i.e. both the  
466 applicant's *Open part* and the API manufacturer's *Restricted part*) is supplied to WHO  
467 directly by the API manufacturer and that the applicant has access to the relevant  
468 information in the APIMF concerning the current manufacture of the API.  
469

470 A copy of the letter of access should be provided in the PD *Module 1*.

471

472 APIMF holders can use the guidance provided for the option “Full details in the PD”  
473 for preparation of the relevant sections of the Open and Restricted parts of their  
474 APIMFs. Reference should also be made to the APIMF guideline in WHO Technical  
475 Report Series, No. 948, Annex 4.

476

477 • *Option 3: Full details in the PD*

478

479 Information on the *3.2.S Active pharmaceutical ingredient* sections, including full  
480 details of chemistry, manufacturing process, quality controls during manufacturing  
481 and process validation for the API, should be submitted in the PD as outlined in the  
482 subsequent sections of this guideline. The QOS-PD should be completed as per  
483 section 3.1 of this guideline.

484

### 485 **3.2.S.1 General information (name, manufacturer)**

486

#### 487 **3.2.S.1.1 Nomenclature (name, manufacturer)**

488

489 **Information on the nomenclature of the API should be provided. For example:**

490

- 491 • **(Recommended) International Nonproprietary Name (INN);**
- 492 • **Compendial name, if relevant;**
- 493 • **Chemical name(s);**
- 494 • **Company or laboratory code;**
- 495 • **Other nonproprietary name(s) (e.g., national name, United States Adopted Name**  
496 **(USAN), British Approved Name (BAN)); and**
- 497 • **Chemical Abstracts Service (CAS) registry number.**

498

499 The listed chemical names should be consistent with those appearing in scientific literature  
500 and those appearing on the product labelling information (e.g. summary of product  
501 characteristics, package leaflet (also known as patient information leaflet or PIL), labelling).  
502 Where several names exist, the preferred name should be indicated.

503

#### 504 **3.2.S.1.2 Structure (name, manufacturer)**

505

506 **The structural formula, including relative and absolute stereochemistry, the molecular**  
507 **formula and the relative molecular mass should be provided.**

508

509 This information should be consistent with that provided in section 3.2.S.1.1. For APIs  
510 existing as salts, the molecular mass of the free base or acid should also be provided.

511

#### 512 **3.2.S.1.3 General properties (name, manufacturer)**

513

514 **A list should be provided of physicochemical and other relevant properties of the API.**

515

516 This information can be used in developing the specifications, in formulating FPPs and in the  
517 testing for release and stability purposes.

518

519 The physical and chemical properties of the API should be discussed including the physical  
520 description, solubilities in common solvents (e.g. water, alcohols, dichloromethane, acetone),  
521 quantitative aqueous pH solubility profile (e.g. pH 1.2 to 6.8, dose/solubility volume),  
522 polymorphism, pH and pKa values, UV absorption maxima and molar absorptivity, melting  
523 point, refractive index (for a liquid), hygroscopicity, partition coefficient, etc (see table in the  
524 QOS-PD). This list is not intended to be exhaustive, but provides an indication as to the type  
525 of information that could be included.

526  
527 Some of the more relevant properties to be considered for APIs are discussed below in greater  
528 detail.

529

### 530 *Physical description*

531

532 The description should include appearance, colour and physical state. Solid forms should be  
533 identified as being crystalline or amorphous (see 3.2.S.3.1 for further information on API  
534 solid forms).

535

### 536 *Solubilities/quantitative aqueous pH solubility profile*

537

538 The following should be provided for all options for the submission of API data.

539

540 The solubilities in a number of common solvents should be provided (e.g. water, alcohols,  
541 dichloromethane, acetone).

542

543 The solubilities over the physiological pH range (pH 1.2 to 6.8) in several buffered media  
544 should be provided in mg/ml. If this information is not readily available (e.g. literature  
545 references), it should be generated in-house.

546

547 For solid oral dosage forms, the dose/solubility volume should be provided as determined by:

548

$$\text{dose/solubility volume} = \frac{\text{largest dosage strength (mg)}}{\text{the minimum concentration of the drug (mg/ml)*}}$$

549

550 \* corresponding to the lowest solubility determined over the physiological pH range (pH 1.2  
551 to 6.8) and temperature ( $37 \pm 0.5$  °C).

552

553 As per the Biopharmaceutics Classification System (BCS), *highly soluble (or highly water-*  
554 *soluble)* APIs are those with a dose/solubility volume of less than or equal to 250 ml.

555

556 For example, compound A has as its lowest solubility at  $37 \pm 0.5$  °C, 1.0 mg/ml at pH 6.8 and  
557 is available in 100 mg, 200 mg and 400 mg strengths. This API would not be considered a  
558 *BCS highly soluble* API as its dose/solubility volume is greater than 250 ml (400 mg/1.0  
559 mg/ml = 400 ml).

560

### 561 *Polymorphism*

562

563 As recommended in ICH's *CTD-Q Questions and answers/location issues* document the  
564 following refers to *where* specific data should be located in the PD:

- 565 • the polymorphic form(s) present in the proposed API should be listed in section  
566 3.2.S.1.3;

- 567       • the description of manufacturing process and process controls (3.2.S.2.2) should  
568       indicate which polymorphic form is manufactured, where relevant;
- 569       • the literature references or studies performed to identify the potential polymorphic  
570       forms of the API, including the study results, should be provided in section 3.2.S.3.1;  
571       and
- 572       • if a polymorphic form is to be defined or limited (e.g. for APIs that are not *BCS highly*  
573       *soluble* and/or where polymorphism has been identified as an issue), details should be  
574       included in 3.2.S.4.1 through 3.2.S.4.5.

575

576       Additional information is included in the referenced sections of this guideline.

577

#### 578       *Particle size distribution*

579

580       As recommended in ICH's *CTD-Q Questions and Answers/Location Issues* document, the  
581       studies performed to identify the particle size distribution of the API should be provided in  
582       section 3.2.S.3.1 (refer to this section of this guideline for additional information).

583

#### 584       *Information from literature*

585

586       Supportive data and results from specific studies or published literature can be included  
587       within or attached to this section.

588

589       Reference documents: ICH Q6A

590

### 591       **3.2.S.2 Manufacture (name, manufacturer)**

592

#### 593       **3.2.S.2.1 Manufacturer(s) (name, manufacturer)**

594

595       **The name, address, and responsibility of each manufacturer, including contractors, and**  
596       **each proposed production site or facility involved in manufacturing and testing should**  
597       **be provided.**

598

599       The facilities involved in the manufacturing, packaging, labelling, testing and storage of the  
600       API should be listed. If certain companies are responsible only for specific steps (e.g. milling  
601       of the API), this should be clearly indicated.

602

603       The list of manufacturers/companies should specify the *actual addresses* of production or  
604       manufacturing site(s) involved (including block(s) and units(s)), rather than the administrative  
605       offices. Telephone number(s), fax number(s) and e-mail address(es) should be provided.

606

607       A valid manufacturing authorization should be provided for the production of APIs. If  
608       available, a certificate of GMP compliance should be provided in the PD in Module 1.

609

#### 610       **3.2.S.2.2 Description of manufacturing process and process controls (name, manufacturer)**

611

612       **The description of the API manufacturing process represents the applicant's**  
613       **commitment for the manufacture of the API. Information should be provided to**  
614       **adequately describe the manufacturing process and process controls. For example,**

615

616 **a flow diagram of the synthetic process(es) should be provided that includes molecular**  
617 **formulae, weights, yield ranges, chemical structures of starting materials, intermediates,**  
618 **reagents and API reflecting stereochemistry, and identifies operating conditions and**  
619 **solvents.**

620  
621 **A sequential procedural narrative of the manufacturing process should be submitted.**  
622 **The narrative should include, for example, quantities of raw materials, solvents,**  
623 **catalysts and reagents reflecting the representative batch scale for commercial**  
624 **manufacture, identification of critical steps, process controls, equipment and operating**  
625 **conditions (e.g. temperature, pressure, pH, time).**  
626

627 **Alternate processes should be explained and described with the same level of detail as**  
628 **the primary process. Reprocessing steps should be identified and justified. Any data to**  
629 **support this justification should be either referenced or filed in 3.2.S.2.5.**  
630

631 Where the APIMF procedure is used, a cross-reference to the Restricted part of the APIMF  
632 may be indicated for confidential information. In this case, if detailed information is  
633 presented in the Restricted part, the information to be provided for this section of the PD  
634 includes a flow chart (including molecular structures and all reagents and solvents) and a brief  
635 outline of the manufacturing process, with special emphasis on the final steps including  
636 purification procedures. However, for sterile APIs full validation data on the sterilization  
637 process should be provided in the Open part (in cases where there is no further sterilization of  
638 the final product).  
639

640 The following requirements apply to the third option for submission of API information,  
641 where full details are provided in the dossier.  
642

643 As discussed in ICH Q7 and WHO Technical Report Series, No. 957 Annex 2, the point at  
644 which the *API starting material* is introduced into the manufacturing process is the starting  
645 point of the application of GMP requirements, according to the above guideline. The *API*  
646 *starting material* itself needs to be proposed and justified by the manufacturer and accepted as  
647 such by assessors. This justification should be documented and be available for review by  
648 WHO GMP inspectors.  
649

650 The *API starting material* should be fully characterized with respect to identity and purity.  
651 The *starting material for synthesis* defines the starting point in the manufacturing process for  
652 an API to be described in an application. The applicant should propose and justify which  
653 substances should be considered as *starting materials for synthesis*. See section 3.2.S.2.3 for  
654 further guidance.  
655

656 In addition to the detailed description of the manufacturing process as per ICH M4Q, the  
657 recovery of materials, if any, should be described in detail with the step in which they are  
658 introduced into the process. Recovery operations should be adequately controlled such that  
659 impurity levels do not increase over time. For recovery of solvents, any processing to  
660 improve the quality of the recovered solvent should be described. Regarding recycling of  
661 filtrates (mother liquors) to obtain second crops, information should be available on maximum  
662 holding times of mother liquors and maximum number of times the material can be recycled.  
663 Data on impurity levels should be provided to justify recycling of filtrates.  
664

665 Where there are multiple manufacturing sites for one API manufacturer, a comprehensive list  
666 in tabular form should be provided comparing the processes at each site and highlighting any  
667 differences.

668  
669 All solvents used in the manufacture (including purification and/or crystallization step(s))  
670 should be clearly identified. Solvents used in the final steps should be of high purity. Use of  
671 recovered solvents in the final steps of purification and/or crystallization is not recommended.  
672

673 Where polymorphic/amorphous forms have been identified, the form resulting from the  
674 synthesis should be stated.

675  
676 Where particle size is considered a critical attribute (see 3.2.S.3.1 for details), the particle size  
677 reduction method(s) (milling, micronization) should be described.

678  
679 Justification should be provided for alternate manufacturing processes. Alternate processes  
680 should be explained with the same level of detail as the primary process. It should be  
681 demonstrated that batches obtained by the alternate processes have the same impurity profile  
682 as the principal process. If the obtained impurity profile is different it should be demonstrated  
683 to be acceptable according to the requirements described under S.3.2.

684  
685 It is acceptable to provide information on pilot scale manufacture, provided it is representative  
686 of production scale and scale-up is reported immediately to WHO according to the  
687 requirements of the WHO variation guideline (reference:: WHO Technical Report Series, No.  
688 943, Annex 6).

689  
690 **3.2.S.2.3 Control of materials (name, manufacturer)**

691  
692 **Materials used in the manufacture of the API (e.g. raw materials, starting materials,**  
693 **solvents, reagents, catalysts) should be listed, identifying where each material is used in**  
694 **the process. Information on the quality and control of these materials should be**  
695 **provided. Information demonstrating that materials meet standards appropriate for**  
696 **their intended use should be provided, as appropriate (details in 3.2.A.2).**

697  
698 Where the APIMF procedure is used, a cross-reference to the Restricted part of the APIMF is  
699 considered sufficient for this section.

700  
701 The following requirements apply to the third option for submission of API information,  
702 where full details are provided in the dossier.

703  
704 In general, the starting material for synthesis described in the PD should:

- 705
- 706 • be a synthetic precursor of one or more synthesis steps prior to the final API  
707 intermediate. Acids, bases, salts, esters and similar derivatives of the API, as well as  
708 the racemate of a single enantiomer API, are not considered final intermediates;
  - 709 • be a well characterized, isolated and purified substance with its structure fully  
710 elucidated including its stereochemistry (when applicable);
  - 711 • have welldefined specifications that include among others one or more specific  
712 identity tests and tests and limits for assay and specified, unspecified and total  
713 impurities; and
  - 714 • be incorporated as a significant structural fragment into the structure of the API.

715  
716 For each starting material, the name and manufacturing site address of the manufacturer  
717 should be indicated. If there are several manufacturers, it should be clarified whether the  
718 starting material obtained from different sources is prepared by the same route of synthesis or  
719 if different routes are used. Specifications proposed for the starting material should apply to  
720 the material from each source.

721  
722 Copies of the specifications for the materials used in the synthesis, extraction, isolation and  
723 purification steps should be provided in the PD, including starting materials, reagents,  
724 solvents, catalysts and recovered materials. Confirmation should be provided that the  
725 specifications apply to materials used at each manufacturing site. A certificate of analysis of  
726 the starting material for synthesis should be provided. A summary of the information on  
727 starting materials should be provided in the QOS-PD.

728  
729 The carry-over of impurities of the starting materials for synthesis into the final API should be  
730 considered and discussed.

731  
732 A letter of attestation should be provided confirming that the API and the starting materials  
733 and reagents used to manufacture the API are *without* risk of transmitting agents of animal  
734 spongiform encephalopathies.

735  
736 When available, a CEP demonstrating TSE-compliance should be provided. A complete copy  
737 of the CEP (including any annexes) should be provided in Module 1.

738  
739 Reference documents: ICH Q6A

#### 740 741 **3.2.S.2.4 Controls of critical steps and intermediates (name, manufacturer)**

742  
743 **Critical steps: Tests and acceptance criteria (with justification including experimental**  
744 **data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing process to**  
745 **ensure that the process is controlled should be provided.**

746  
747 **Intermediates: Information on the quality and control of intermediates isolated during**  
748 **the process should be provided.**

749  
750 Where the APIMF procedure is used a cross-reference to the Restricted part of the APIMF is  
751 considered sufficient for this section of the PD, with the exception of information that is also  
752 relevant for the applicant (reference: APIMF guideline in WHO Technical Report Series, No.  
753 948, Annex 4).

754  
755 The following requirements apply to the third option for submission of API information,  
756 where full details are provided in the dossier.

757  
758 The critical steps should be identified. These can be among others: steps where significant  
759 impurities are removed or introduced, steps introducing an essential molecular structural  
760 element such as a chiral centre or resulting in a major chemical transformation, steps having  
761 an impact on solid-state properties and homogeneity of the API that may be relevant for use in  
762 solid dosage forms.

763  
764 Specifications for isolated intermediates should be provided and should include tests and  
765 acceptance criteria for identity, purity and assay, where applicable.

766

767 Reference documents: ICH Q6A

768

769 **3.2.S.2.5 Process validation and/or evaluation (name, manufacturer)**

770

771 **Process validation and/or evaluation studies for aseptic processing and sterilization**  
772 **should be included.**

773

774 Where the APIMF procedure is used, a cross-reference to the Restricted part of the APIMF is  
775 considered sufficient for this section of the PD.

776

777 The following requirements apply to the third option for submission of API information,  
778 where full details are provided in the dossier.

779

780 It is expected that the manufacturing processes for all APIs are properly controlled. If the API  
781 is prepared as sterile, a complete description should be provided for aseptic processing and/or  
782 sterilization methods. The controls used to maintain the sterility of the API during storage and  
783 transportation should also be provided. Alternate processes should be justified and described  
784 (see guidance in 3.2.S.2.2 for the level of detail expected).

785

786 **3.2.S.2.6 Manufacturing process development (name, manufacturer)**

787

788 **A description and discussion should be provided of the significant changes made to the**  
789 **manufacturing process and/or manufacturing site of the API used in producing**  
790 **comparative bioavailability or biowaiver, scale-up pilot and, if available, production**  
791 **scale batches.**

792

793 **Reference should be made to the API data provided in section 3.2.S.4.4.**

794

795 Where the APIMF procedure is used, a cross-reference to the Restricted part of the APIMF is  
796 considered sufficient for this section of the PD.

797

798 **3.2.S.3 Characterization (name, manufacturer)**

799

800 **3.2.S.3.1 Elucidation of structure and other characteristics (name, manufacturer)**

801

802 **Confirmation of structure based on e.g. synthetic route and spectral analyses should be**  
803 **provided. Information such as the potential for isomerism, the identification of**  
804 **stereochemistry or the potential for forming polymorphs should also be included.**

805

806 *Elucidation of structure*

807

808 The PD should include quality assurance (QA) certified copies of the spectra, peak  
809 assignments and a detailed interpretation of the data of the studies performed to elucidate  
810 and/or confirm the structure of the API. The QOS-PD should include a list of the studies  
811 performed and a conclusion from the studies (e.g. if the results support the proposed  
812 structure).

813

814 For APIs that are not described in an officially recognized pharmacopoeia, the studies carried  
815 out to elucidate and/or confirm the chemical structure normally include elemental analysis,  
816 infrared (IR), ultraviolet (UV), nuclear magnetic resonance (NMR) and mass spectra (MS)

817 studies. Other tests could include X-ray powder diffraction (XRPD) and differential scanning  
818 calorimetry (DSC).

819

820 For APIs that are described in an officially recognized pharmacopoeia, it is generally  
821 sufficient to provide copies of the IR spectrum of the API from each of the proposed  
822 manufacturer(s) run concomitantly with a pharmacopoeial reference standard. See section  
823 3.2.S.5 for details on acceptable reference standards or materials.

824

825 *Isomerism/Stereochemistry*

826

827 **When an API is chiral, it should be specified whether specific stereoisomers or a mixture**  
828 **of stereoisomers have been used in the comparative biostudies, and information should**  
829 **be given as to the stereoisomer of the API that is to be used in the FPP.**

830

831 Where the potential for stereoisomerism exists, a discussion should be included of the  
832 possible isomers that can result from the manufacturing process and the steps where chirality  
833 was introduced. The identity of the isomeric composition of the API to that of the API in  
834 the comparator product should be established. Information on the physical and chemical  
835 properties of the isomeric mixture or single enantiomer should be provided, as appropriate.  
836 The API specification should include a test to ensure isomeric identity and purity.

837

838 The potential for interconversion of the isomers in the isomeric mixture, or racemisation of  
839 the single enantiomer should be discussed.

840

841 When a single enantiomer of the API is claimed for nonpharmacopoeial APIs, unequivocal  
842 proof of absolute configuration of asymmetric centres should be provided such as determined  
843 by X-ray of a single crystal.

844

845 If, based on the structure of the API, there is not a potential for stereoisomerism, it is  
846 sufficient to include a statement to this effect.

847

848 *Polymorphism*

849

850 Many APIs can exist in different physical forms in the solid state. Polymorphism is  
851 characterized as the ability of an API to exist as two or more crystalline phases that have  
852 different arrangements and/or conformations of the molecules in the crystal lattice.  
853 Amorphous solids consist of disordered arrangements of molecules and do not possess a  
854 distinguishable crystal lattice. Solvates are crystal forms containing either stoichiometric or  
855 nonstoichiometric amounts of a solvent. If the incorporated solvent is water the solvates are  
856 also commonly known as hydrates.

857

858 Polymorphic forms of the same chemical compound differ in internal solid-state structure  
859 and, therefore, may possess different chemical and physical properties, including packing,  
860 thermodynamic, spectroscopic, kinetic, interfacial and mechanical properties. These  
861 properties can have a direct impact on API processability, pharmaceutical product  
862 manufacturability and product quality/performance, including stability, dissolution and  
863 bioavailability. Unexpected appearance or disappearance of a polymorphic form may lead to  
864 serious pharmaceutical consequences.

865

866 Applicants to the Prequalification Programme and API manufacturers are expected to have  
867 adequate knowledge about the polymorphism of the APIs used and/or produced. Information

868 on polymorphism can come from the scientific literature, patents, compendia or other  
869 references to determine if polymorphism is a concern, e.g. for APIs that are not *BCS highly*  
870 *soluble*. In the absence of published data for APIs that are not *BCS highly soluble*,  
871 polymorphic screening will be necessary to determine if the API can exist in more than one  
872 crystalline form. Polymorphic screening is generally accomplished via crystallization studies  
873 using different solvents and conditions.

874  
875 There are a number of methods that can be used to characterize the polymorphic forms of an  
876 API. Demonstration of a nonequivalent structure by single crystal X-ray diffraction is  
877 currently regarded as the definitive evidence of polymorphism. XRPD can also be used to  
878 provide unequivocal proof of polymorphism. Other methods, including microscopy, thermal  
879 analysis (e.g. DSC, thermal gravimetric analysis and hot-stage microscopy) and spectroscopy  
880 (e.g. IR, Raman, solid-state nuclear magnetic resonance (ssNMR]) are helpful to further  
881 characterize polymorphic forms. Where polymorphism is a concern, the applicants/  
882 manufacturers of APIs should demonstrate that a suitable method, capable of distinguishing  
883 different polymorphs, is available to them.

884  
885 Decision tree 4(1) of ICH Q6A can be used where screening is necessary and 4(2) can be used  
886 to investigate if different polymorphic forms have different properties that may affect  
887 performance, bioavailability and stability of the FPP and to decide whether a preferred  
888 polymorph should be monitored at release and on storage of the API. Where there is a  
889 preferred polymorph, acceptance criteria should be incorporated into the API specification to  
890 ensure polymorphic equivalence of the commercial material and that of the API batches used  
891 in the comparative bioavailability or biowaiver studies. The polymorphic characterization of  
892 the API batches used in comparative bioavailability or biowaiver studies by the above-  
893 mentioned methods should be provided. The method used to control polymorphic form  
894 should be demonstrated to be specific for the preferred form.

895  
896 Polymorphism can also include solvation or hydration products (also known as  
897 pseudopolymorphs). If the API is used in a solvated form, the following information should  
898 be provided:

- 899
- 900 • specifications for the solvent-free API in 3.2.S.2.4, if that compound is a synthetic
  - 901 precursor;
  - 902 • specifications for the solvated API including appropriate limits on the weight ratio of
  - 903 API to solvent (with data to support the proposed limits);
  - 904 • a description of the method used to prepare the solvate in 3.2.S.2.2.
- 905

#### 906 *Particle size distribution*

907

908 For APIs that are not *BCS highly soluble* contained in solid FPPs, or liquid FPPs containing  
909 undissolved API, the particle size distribution of the material can have an effect on the in vitro  
910 and/or in vivo behaviour of the FPP. Particle size distribution can also be important in dosage  
911 form performance (e.g. delivery of inhalation products), achieving uniformity of content in  
912 low-dose tablets (e.g. 2 mg or less), desired smoothness in ophthalmic preparations and  
913 stability of suspensions.

- 914
- 915 • If particle size distribution is an important parameter (e.g. as in the above cases),
  - 916 results from an investigation of several batches of the API should be provided,
  - 917 including characterization of the batch(es) used in the comparative bioavailability or

918 biowaiver studies. API specifications should include controls on the particle size  
919 distribution to ensure consistency with the material in the batch(es) used in the  
920 comparative bioavailability and biowaiver studies (e.g. limits for d10, d50 and d90).  
921 The criteria should be established statistically based on the standard deviation of the  
922 test results from the previously mentioned studies. The following is provided for  
923 illustrative purposes as possible acceptance criteria for particle size distribution limits:

- 924 • d10 not more than (NMT) 10% of total volume less than X  $\mu\text{m}$
- 925 • d50 XX  $\mu\text{m}$  – XXX  $\mu\text{m}$
- 926 • d90 not less than (NLT) 90% of total volume less than XXXX  $\mu\text{m}$ .

927  
928 Other controls on particle size distribution can be considered acceptable, if scientifically  
929 justified.

930  
931 Reference documents: ICH Q6A

### 932 933 3.2.S.3.2 *Impurities (name, manufacturer)*

934  
935 **Information on impurities should be provided.**

936  
937 Details on the principles for the control of impurities (e.g. reporting, identification and  
938 qualification) are outlined in the ICH Q3A, Q3B and Q3C impurity guidelines. Additional  
939 information to provide further guidance on some of the elements discussed in the ICH  
940 guidelines is outlined below.

941  
942 Regardless of whether a pharmacopoeial standard is claimed, a discussion should be provided  
943 of the potential and actual impurities arising from the synthesis, manufacture or degradation  
944 of the API. This should cover starting materials, by-products, intermediates, chiral impurities  
945 and degradation products and should include the chemical names, structures and origins. The  
946 discussion of pharmacopoeial APIs should not be limited to the impurities specified in the  
947 API monograph.

948  
949 The tables in the QOS-PD template should be used to summarize the information on the API-  
950 related and process-related impurities. In the QOS-PD, the term *origin* refers to how and  
951 where the impurity was introduced (e.g. “Synthetic intermediate from Step 4 of the  
952 synthesis”, “Potential by-product due to rearrangement from Step 6 of the synthesis”). It  
953 should also be indicated if the impurity is a metabolite of the API.

954  
955 The ICH thresholds for reporting, identification (used to set the limit for individual unknown  
956 impurities) and qualification are determined on the basis of potential exposure to the impurity,  
957 e.g. by the maximum daily dose (MDD) of the API. For APIs available in multiple dosage  
958 forms and strengths having different MDD values, it is imperative that the thresholds and  
959 corresponding controls for each of the presentations be considered to ensure that the risks  
960 posed by impurities have been addressed. This is normally achieved by using the *highest*  
961 *potential daily MDD*, rather than the *maintenance dose*. For parenteral products the maximum  
962 hourly dose of the API should also be included.

963  
964 It is acknowledged that APIs of semisynthetic origin do not fall within the scope of the ICH  
965 impurity guidelines. However, depending on the nature of the API and the extent of the  
966 chemical modification steps, the *principles* on the control of impurities (e.g. reporting,  
967 identification and qualification) could also be extended to APIs of semisynthetic origin. As an

968 illustrative example, an API whose precursor molecule was derived from a fermentation  
969 process, or a natural product of plant or animal origin that has subsequently undergone *several*  
970 chemical modification reactions generally would fall within this scope, whereas an API whose  
971 sole chemical step was the formation of a salt from a fermentation product generally would  
972 not fall within this scope. It is understood that there is some latitude for these types of APIs.  
973

#### 974 *Identification of impurities*

975  
976 It is recognized by the pharmacopoeias that APIs can be obtained from various sources and  
977 thus can contain impurities not considered during the development of the monograph.  
978 Furthermore, a change in the production or source may give rise to additional impurities that  
979 are not adequately controlled by the official compendial monograph. As a result, each PD is  
980 assessed independently to consider the potential impurities that may arise from the proposed  
981 route(s) of synthesis. For these reasons the ICH limits for unspecified impurities (e.g. NMT  
982 0.10% or 1.0 mg per day intake (whichever is lower) for APIs having a maximum daily dose  
983  $\leq 2$  g/day) are generally recommended, rather than the general limits for unspecified impurities  
984 that may appear in the official compendial monograph that could potentially be higher than  
985 the applicable ICH limit.  
986

#### 987 *Qualification of impurities*

988  
989 The ICH impurity guidelines should be consulted for options on the qualification of  
990 impurities. The limit specified for an identified impurity in an *officially recognized*  
991 *pharmacopoeia* is generally considered to be qualified. The following is an additional option  
992 for qualification of impurities in existing APIs:

993       The limit for an impurity present in an existing API can be accepted by comparing the  
994 impurity results found in the existing API with those observed in an innovator product  
995 using the same validated, stability-indicating analytical procedure (e.g. comparative  
996 HPLC studies). If samples of the innovator product are not available, the impurity  
997 profile may also be compared to a different prequalified FPP with the same route of  
998 administration and similar characteristics (e.g. tablet versus capsule). It is  
999 recommended that the studies be conducted on comparable samples (e.g. age of  
1000 samples) to obtain a meaningful comparison of the impurity profiles.

1001       Levels of impurities generated from studies under accelerated or stressed storage  
1002 conditions of the innovator or prequalified FPP are not considered  
1003 acceptable/qualified.

1004       A specified impurity present in the existing API is considered qualified if the amount  
1005 of the impurity in the existing API reflects the levels observed in the innovator or  
1006 prequalified FPP.  
1007

#### 1008 *Basis for setting the acceptance criteria*

1009  
1010 The basis for setting the acceptance criteria for the impurities should be provided. This is  
1011 established by considering the identification and qualification thresholds for API-related  
1012 impurities (e.g. starting materials, by-products, intermediates, chiral impurities or degradation  
1013 products) and the concentration limits for process-related impurities (e.g. residual solvents) as  
1014 per the applicable ICH guidelines (e.g. Q3A, Q3C).  
1015

1016 The qualified level should be considered as the maximum allowable limit. However, limits  
1017 which are considerably wider than the actual manufacturing process capability are  
1018 generally discouraged. For this reason, the acceptance criteria are also set taking into  
1019 consideration the actual levels of impurities found in several batches of the API from each  
1020 manufacturer, including the levels found in the batches used for the comparative  
1021 bioavailability or biowaiver studies. When reporting the results of quantitative tests, the actual  
1022 numerical results should be provided rather than vague statements such as “within limits” or  
1023 “conforms”. In the cases where a large number of batches have been tested it is acceptable to  
1024 summarize the results of the total number of batches tested with a range of analytical results.  
1025

1026 If there are identified impurities specified in an official compendial monograph that are not  
1027 controlled by the proposed routine in-house analytical procedure, a justification for their  
1028 exclusion from routine analyses should be provided (e.g. “Impurities D, E and F listed in the  
1029 Ph.Int. monograph are not potential impurities from the proposed route of synthesis used by  
1030 manufacturer X”). If acceptable justification cannot be provided it should be demonstrated  
1031 that the routine in-house method is capable of separating and detecting the impurities  
1032 specified in the official compendial monograph at an acceptable level (e.g. 0.10%). If such a  
1033 demonstration cannot be performed, a one-time study should be conducted applying the  
1034 pharmacopoeial method to several recent batches to demonstrate the absence of the  
1035 pharmacopoeial listed impurities.  
1036

1037 ICH class II solvent(s) used prior to the last step of the manufacturing process may be  
1038 exempted from routine control in API specifications if suitable justification is provided.  
1039 Submission of results demonstrating less than 10% of the ICH Q3C limit (option I) of the  
1040 solvent(s) in three consecutive production-scale batches or six consecutive pilot-scale batches  
1041 of the API or a suitable intermediate would be considered acceptable justification. The last  
1042 step solvents used in the process should always be routinely controlled in the final API.  
1043

1044 For guidance on acceptable residual solvent limits refer to ICH Q3C. The limit for residues of  
1045 triethylamine (TEA) is either 320 ppm on the basis of ICH Q3C option I or 3.2 mg/day on the  
1046 basis of permitted daily exposure (PDE).  
1047

1048 The absence of known established highly toxic impurities (genotoxic) used in the process or  
1049 formed as a by-product should be discussed and suitable limits should be proposed. The limits  
1050 should be justified by appropriate reference to available guidances (e.g. EMEA/CHMP/QWP/  
1051 251344/2006 or USFDA Guidance for Industry: Genotoxic and carcinogenic impurities in  
1052 drug substances and products, recommended approaches, December 2008) or by providing  
1053 experimental safety data or published data in peer-reviewed journals.  
1054

1055 Residues of metal catalysts used in the manufacturing process and determined to be present in  
1056 batches of API are to be controlled in specifications. This requirement does not apply to  
1057 metals that are deliberate components of the pharmaceutical substance (such as a counter ion  
1058 of a salt) or metals that are used as a pharmaceutical excipient in the FPP (e.g. an iron oxide  
1059 pigment). The guideline on the specification limits for residues of metal catalysts or metal  
1060 reagents EMEA/CHMP/SWP/4446/2000 or any equivalent approaches can be used to address  
1061 this issue. The requirement normally does not apply to extraneous metal contaminants that are  
1062 more appropriately addressed by GMP, good distribution practices (GDP) or any other  
1063 relevant quality provision such as the heavy metal test in monographs of recognized  
1064 pharmacopoeias that cover metal contamination originating from manufacturing equipment  
1065 and the environment.  
1066

1067 Reference documents: ICH Q3A, Q3C, Q6A

1068

1069 **3.2.S.4 Control of the API (name, manufacturer)**

1070

1071 **3.2.S.4.1 Specification (name, manufacturer)**

1072

1073 **The specification for the API should be provided.**

1074

1075 As defined in ICH's Q6A guideline, a specification is:

1076 *“a list of tests, references to analytical procedures and appropriate acceptance*  
1077 *criteria, which are numerical limits, ranges, or other criteria for the tests described. It*  
1078 *establishes the set of criteria to which an API or FPP should conform to be*  
1079 *considered acceptable for its intended use. “Conformance to specifications” means*  
1080 *that the API and / or FPP, when tested according to the listed analytical procedures,*  
1081 *will meet the listed acceptance criteria. Specifications are critical quality standards*  
1082 *that are proposed and justified by the manufacturer and approved by regulatory*  
1083 *authorities.”*

1084

1085 Copies of the API specifications, dated and signed by authorized personnel (e.g. the person in  
1086 charge of the quality control or quality assurance department) should be provided in the PD,  
1087 including specifications from each API manufacturer as well as those of the FPP  
1088 manufacturer.

1089

1090 The FPP manufacturer's API specification should be summarized according to the table in the  
1091 QOS-PD template under the headings tests, acceptance criteria and analytical procedures  
1092 (including types, sources and versions for the methods).

1093

- 1094 • The *standard* declared by the applicant could be an officially recognized compendial  
1095 standard (e.g. BP, JP, Ph.Eur, Ph.Int., USP) or a house (manufacturer's) standard.
- 1096 • The *specification reference number and version* (e.g. *revision number and/or date*)  
1097 should be provided for version control purposes.
- 1098 • For the analytical procedures, the *type* should indicate the kind of analytical procedure  
1099 used (e.g. visual, IR, UV, HPLC, laser diffraction), the *source* refers to the origin of  
1100 the analytical procedure (e.g. BP, JP, Ph.Eur, Ph.Int., USP, in-house) and the *version*  
1101 (e.g. *code number/version/date*) should be provided for version control purposes.

1102

1103 In cases where there is more than one API manufacturer, the FPP manufacturer's API  
1104 specifications should be one single compiled set of specifications that is identical for each  
1105 manufacturer. It is acceptable to lay down in the specification more than one acceptance  
1106 criterion and/or analytical method for a single parameter with the statement “for API from  
1107 manufacturer A” (e.g. in the case of residual solvents).

1108

1109 Any non-routine testing should be clearly identified as such and justified along with the  
1110 proposal on the frequency of non-routine testing.

1111

1112 The ICH Q6A guideline outlines recommendations for a number of *universal* and *specific*  
1113 *tests* and criteria for APIs.

1114

1115 Reference documents: ICH Q3A, Q3C, Q6A, *officially recognized pharmacopoeia*

1116

1117 **3.2.S.4.2 Analytical procedures (name, manufacturer)**

1118

1119 **The analytical procedures used for testing the API should be provided.**

1120

1121 Copies of the in-house analytical procedures used to generate testing results provided in the  
1122 PD, as well as those proposed for routine testing of the API by the FPP manufacturer, should  
1123 be provided. Unless modified, it is not necessary to provide copies of officially recognized  
1124 compendial analytical procedures.

1125

1126 Tables for summarizing a number of the different analytical procedures and validation  
1127 information (e.g. HPLC assay/impurity methods, GC methods) can be found in the 2.3.R  
1128 Regional information section of the QOS-PD (i.e. 2.3.R.2). These tables should be used to  
1129 summarize the in-house analytical procedures *of the FPP manufacturer* for determination of  
1130 the residual solvents, assay and purity of the API, in section 2.3.S.4.2 of the QOS-PD. Other  
1131 methods used to generate assay and purity data in the PD can be summarized in 2.3.S.4.4 (c)  
1132 or 2.3.S.7.3 (b) of the QOS-PD. Officially recognized compendial methods need not be  
1133 summarized unless modifications have been made.

1134

1135 Although HPLC is normally considered the method of choice for determining API-related  
1136 impurities, other chromatographic methods such as GC and TLC can also be used, if  
1137 appropriately validated. For determination of related substances, reference standards should  
1138 normally be available for each of the identified impurities, particularly those known to be  
1139 toxic and the concentration of the impurities should be quantitated against their own reference  
1140 standards. Impurity standards may be obtained from pharmacopoeias (individual impurities  
1141 or resolution mixtures), from commercial sources or prepared in-house. It is considered  
1142 acceptable to use the API as an external standard to estimate the levels of impurities, provided  
1143 the response factors of those impurities are sufficiently close to that of the API, i.e. between  
1144 80 and 120%. In cases where the response factor is outside this range, it may still be  
1145 acceptable to use the API, provided a correction factor is applied. Data to support calculation  
1146 of the correction factor should be provided for an in-house method. Unspecified impurities  
1147 may be quantitated using a solution of the API as the reference standard at a concentration  
1148 corresponding to the limit established for individual unspecified impurities (e.g. 0.10%). The  
1149 test for related substances in the Ph.Int. monograph for lamivudine serves as a typical  
1150 example.

1151

1152 The system suitability tests (SSTs) represent an integral part of the method and are used to  
1153 ensure the adequate performance of the chosen chromatographic system. As a minimum,  
1154 HPLC and GC purity methods should include SSTs for resolution and repeatability. For  
1155 HPLC methods to control API-related impurities, this is typically done using a solution of the  
1156 API with a concentration corresponding to the limit for unspecified impurities. Resolution of  
1157 the two closest eluting peaks is generally recommended. However, the choice of alternate  
1158 peaks can be used if justified (e.g. choice of a toxic impurity). In accordance with the Ph.Int.  
1159 section on *Methods of analysis*, the repeatability test should include an acceptable number of  
1160 replicate injections. HPLC assay methods should include SSTs for repeatability and in  
1161 addition either peak asymmetry, theoretical plates or resolution. For TLC methods, the SSTs  
1162 should verify the ability of the system to separate and detect the analyte(s) (e.g. by applying a  
1163 spot corresponding to the API at a concentration corresponding to the limit of unspecified  
1164 impurities).

1165

1166 Reference documents: ICH Q2, WHO Technical Report Series, No. 943, Annex 3

1167

1168 **3.2.S.4.3 Validation of analytical procedures (name, manufacturer)**

1169

1170 **Analytical validation information, including experimental data for the analytical**  
1171 **procedures used for testing the API, should be provided.**

1172

1173 Copies of the validation reports for the analytical procedures used to generate testing results  
1174 provided in the PD, as well as those proposed for routine testing of the API by the FPP  
1175 manufacturer, should be provided.

1176

1177 Tables for summarizing a number of the different analytical procedures and validation  
1178 information (e.g. HPLC assay/impurity methods, GC methods) can be found in the 2.3.R  
1179 Regional information section of the QOS-PD (i.e. 2.3.R.2). These tables should be used to  
1180 summarize the validation information of the analytical procedures *of the FPP manufacturer*  
1181 for determination of residual solvents, assay and purity of the API, in section 2.3.S.4.3 of the  
1182 QOS-PD. The validation data for other methods used to generate assay and purity data in the  
1183 PD can be summarized in 2.3.S.4.4 (c) or 2.3.S.7.3 (b) of the QOS-PD.

1184

1185 As recognized by regulatory authorities and pharmacopoeias themselves, verification of  
1186 compendial methods can be necessary. The compendial methods as published are typically  
1187 validated based on an API or an FPP originating from a specific manufacturer. Different  
1188 sources of the same API or FPP can contain impurities and/or degradation products that were  
1189 not considered during the development of the monograph. Therefore, the monograph and  
1190 compendial method should be demonstrated suitable to control the impurity profile of the API  
1191 from the intended source(s).

1192

1193 In general verification is not necessary for compendial API *assay* methods. However,  
1194 specificity of a specific compendial assay method should be demonstrated if there are any  
1195 potential impurities that are not specified in the compendial monograph. If an officially  
1196 recognized compendial method is used to control API-related impurities that are not specified  
1197 in the monograph, full validation of the method is expected with respect to those impurities.

1198

1199 If an officially recognized compendial standard is claimed and an in-house method is used in  
1200 lieu of the compendial method (e.g. for assay or for specified impurities), equivalency of the  
1201 in-house and compendial methods should be demonstrated. This could be accomplished by  
1202 performing duplicate analyses of one sample by both methods and providing the results from  
1203 the study. For impurity methods, the sample analyzed should be the API spiked with  
1204 impurities at concentrations equivalent to their specification limits.

1205

1206 Reference documents: ICH Q2

1207

1208 **3.2.S.4.4 Batch analyses (name, manufacturer)**

1209

1210 **Description of batches and results of batch analyses should be provided.**

1211

1212 The information provided should include batch number, batch size, date and production site of  
1213 relevant API batches used in comparative bioavailability or biowaiver studies, preclinical and  
1214 clinical data (if relevant), stability, pilot, scale-up and, if available, production-scale batches.  
1215 This data is used to establish the specifications and evaluate consistency in API quality.

1216

1217 Analytical results should be provided from at least two batches of at least pilot scale from  
1218 each proposed manufacturing site of the API and should include the batch(es) used in the

1219 comparative bioavailability or biowaiver studies. A pilot-scale batch should be manufactured  
1220 by a procedure fully representative of and simulating that to be applied to a full production-  
1221 scale batch.

1222  
1223 Copies of the certificates of analysis, both from the API manufacturer(s) and the FPP  
1224 manufacturer, should be provided for the profiled batches and any company responsible for  
1225 generating the test results should be identified. The FPP manufacturer's test results should be  
1226 summarized in the QOS-PD.

1227  
1228 The discussion of results should focus on observations noted for the various tests, rather than  
1229 reporting comments such as "all tests meet specifications". For quantitative tests (e.g.  
1230 individual and total impurity tests and assay tests), it should be ensured that actual *numerical*  
1231 *results* are provided rather than vague statements such as "within limits" or "conforms".

1232  
1233 A discussion and justification should be provided for any incomplete analyses (e.g. results not  
1234 tested according to the proposed specification).

1235  
1236 Reference documents: ICH Q3A, Q3C, Q6A

1237  
1238 **3.2.S.4.5 Justification of specification (name, manufacturer)**

1239  
1240 **Justification for the API specification should be provided.**

1241  
1242 A discussion should be provided on the inclusion of certain tests, evolution of tests, analytical  
1243 procedures and acceptance criteria, differences from the officially recognized compendial  
1244 standard(s), etc. If the officially recognized compendial methods have been modified or  
1245 replaced, a discussion should be included.

1246  
1247 The justification for certain tests, analytical procedures and acceptance criteria may have been  
1248 discussed in other sections of the PD (e.g. impurities, particle-size distribution) and does not  
1249 need to be repeated here, although a cross-reference to their location should be provided.

1250  
1251 Reference documents: ICH Q3A, Q3C, Q6A, *officially recognized pharmacopoeia*

1252  
1253 **3.2.S.5 Reference standards or materials (name, manufacturer)**

1254  
1255 **Information on the reference standards or reference materials used for testing of the**  
1256 **API should be provided.**

1257  
1258 Information should be provided on the reference standard(s) used to generate data in the PD,  
1259 as well as those to be used by the FPP manufacturer in routine API and FPP testing.

1260  
1261 The source(s) of the reference standards or materials used in the testing of the API should be  
1262 provided (e.g. those used for the identification, purity, assay tests). These could be classified  
1263 as *primary* or *secondary* reference standards.

1264  
1265 A suitable primary reference standard should be obtained from an officially recognized  
1266 pharmacopoeial source (e.g. BP, JP, Ph.Eur, Ph.Int., USP) where one exists and the lot  
1267 number should be provided. Where a pharmacopoeial standard is claimed for the API and/or  
1268 the FPP, the primary reference standard should be obtained from that pharmacopoeia when

1269 available. Primary reference standards from officially recognized pharmacopoeial sources do  
1270 not need further structural elucidation.

1271

1272 Otherwise a primary standard may be a batch of the API that has been fully characterized (e.g.  
1273 by IR, UV, NMR, MS analyses). Further purification techniques may be needed to render the  
1274 material acceptable for use as a chemical reference standard. The purity requirements for a  
1275 chemical reference substance depend upon its intended use. A chemical reference substance  
1276 proposed for an identification test does not require meticulous purification, since the presence  
1277 of a small percentage of impurities in the substance often has no noticeable effect on the test.  
1278 On the other hand, chemical reference substances that are to be used in assays should possess  
1279 a high degree of purity (such as 99.5% on the dried or water-/solvent-free basis). Absolute  
1280 content of the primary reference standard must be declared and should follow the scheme:  
1281 100% minus organic impurities (quantitated by an assay procedure, e.g. HPLC, DSC, etc.)  
1282 minus inorganic impurities minus volatile impurities by loss on drying (or water content  
1283 minus residual solvents).

1284

1285 A secondary (or in-house) reference standard can be used by establishing it against a suitable  
1286 primary reference standard, e.g. by providing legible copies of the IR of the primary and  
1287 secondary reference standards run concomitantly and by providing its certificate of analysis,  
1288 including assay determined against the primary reference standard. A secondary reference  
1289 standard is often characterized and evaluated for its intended purpose with additional  
1290 procedures other than those used in routine testing (e.g. if additional solvents are used during  
1291 the additional purification process that are not used for routine purposes).

1292

1293 Reference standards should normally be established for specified impurities. Refer to  
1294 3.2.S.4.2 for additional guidance.

1295

1296 Reference documents: ICH Q6A, WHO Technical Report Series, No. 943, Annex 3

1297

### 1298 **3.2.S.6 Container-closure system (name, manufacturer)**

1299

1300 **A description of the container-closure system(s) should be provided, including the**  
1301 **identity of materials of construction of each primary packaging component, and their**  
1302 **specifications. The specifications should include description and identification (and**  
1303 **critical dimensions with drawings, where appropriate). Noncompendial methods (with**  
1304 **validation) should be included, where appropriate.**

1305

1306 **For nonfunctional secondary packaging components (e.g. those that do not provide**  
1307 **additional protection), only a brief description should be provided. For functional**  
1308 **secondary packaging components, additional information should be provided.**

1309

1310 **The suitability should be discussed with respect to, for example, choice of materials,**  
1311 **protection from moisture and light, compatibility of the materials of construction with**  
1312 **the API, including sorption to container and leaching, and/or safety of materials of**  
1313 **construction.**

1314

1315 The WHO *Guidelines on packaging for pharmaceutical products* (WHO Technical Report  
1316 Series, No. 902, Annex 9, 2002) and the officially recognized pharmacopoeias should be  
1317 consulted for recommendations on the packaging information for APIs.

1318

1319 Primary packaging components are those that are in direct contact with the API or FPP. The  
1320 specifications for the primary packaging components should be provided and should include a  
1321 specific test for identification (e.g. IR).

1322  
1323 Copies of the labels applied on the secondary packaging of the API should be provided and  
1324 should include the conditions of storage. In addition, the name and address of the  
1325 manufacturer of the API should be stated on the container, regardless of whether relabelling is  
1326 conducted at any stage during the API distribution process.

1327  
1328 **3.2.S.7 Stability (name, manufacturer)**

1329  
1330 **3.2.S.7.1 Stability summary and conclusions (name, manufacturer)**

1331  
1332 **The types of studies conducted, protocols used and the results of the studies should be**  
1333 **summarized. The summary should include results, for example, from forced**  
1334 **degradation studies and stress conditions, as well as conclusions with respect to storage**  
1335 **conditions and re-test date or shelf-life, as appropriate.**

1336  
1337 The WHO guideline *Stability testing of active pharmaceutical ingredients and finished*  
1338 *pharmaceutical products* (WHO Technical Report Series, No. 953, Annex 2) should be  
1339 consulted for recommendations on the core stability data package required for the  
1340 prequalification of APIs and FPPs.

1341  
1342 As outlined in the WHO stability guideline, the purpose of stability testing is to:

1343 *“provide evidence of how the quality of an API or FPP varies with time under the*  
1344 *influence of a variety of environmental factors such as temperature, humidity and*  
1345 *light.”*

1346  
1347 The tables in the QOS-PD template should be used to summarize the results from the stability  
1348 studies and related information (e.g. conditions, testing parameters, conclusions,  
1349 commitments).

1350  
1351 *Stress testing*

1352  
1353 As outlined in the ICH Q1A guidance document, stress testing of the API can help identify  
1354 the likely degradation products, which can in turn help establish the degradation pathways and  
1355 the intrinsic stability of the molecule and validate the stability indicating power of the  
1356 analytical procedures used. The nature of the stress testing will depend on the individual API  
1357 and the type of FPP involved.

1358  
1359 Stress testing may be carried out on a single batch of the API. For examples of typical stress  
1360 conditions refer to WHO Technical Report Series, No. 953, Annex 2, section 2.1.2, as well as  
1361 “A typical set of studies of the degradation paths of an active pharmaceutical ingredient” in  
1362 WHO Technical Report Series, No. 929, Annex 5, Table A.1.

1363  
1364 The objective of stress testing is not to completely degrade the API, but to cause degradation  
1365 to occur to a small extent, typically 10–30% loss of active by assay when compared with non-  
1366 degraded API. This target is chosen so that some degradation occurs, but not enough to  
1367 generate secondary products. For this reason, the conditions and duration may need to be  
1368 varied when the API is especially susceptible to a particular stress factor. In the total absence

1369 of degradation products after 10 days, the API is considered stable under the particular stress  
1370 condition.

1371

1372 The tables in the QOS-PD template should be used to summarize the results of the stress  
1373 testing and should include the treatment conditions (e.g. temperatures, relative humidities,  
1374 concentrations of solutions, durations) and the observations for the various test parameters  
1375 (e.g. assay, degradation products). The discussion of results should highlight whether mass  
1376 balance was observed.

1377

1378 Photostability testing should be an integral part of stress testing. The standard conditions are  
1379 described in ICH Q1B. If “protect from light” is stated in one of the officially recognized  
1380 pharmacopoeia for the API, it is sufficient to state “protect from light” on labelling, in lieu of  
1381 photostability studies, when the container-closure system is shown to be light-protective.

1382

1383 When available, it is acceptable to provide the relevant data published in the scientific  
1384 literature (inter alia WHOPARs, EPARs) to support the identified degradation products and  
1385 pathways.

1386

#### 1387 *Accelerated and long-term testing*

1388

1389 Available information on the stability of the API under accelerated and long-term conditions  
1390 should be provided, including information in the public domain or obtained from scientific  
1391 literature. The source of the information should be identified.

1392

1393 The required long-term storage conditions for APIs in the Prequalification Programme is  
1394 either 30 °C±2 °C/65%±5%RH or 30 °C±2 °C/75%±5%RH. Studies covering the proposed  
1395 re-test period at the above-mentioned long-term storage conditions will provide better  
1396 assurance of the stability of APIs at the conditions of the supply chain corresponding to the  
1397 WHO and Prequalification Programme environments. Alternative conditions should be  
1398 supported with appropriate evidence, which may include literature references or in-house  
1399 studies, demonstrating that storage at 30 °C is inappropriate for the API. For APIs intended  
1400 for storage in a refrigerator and those intended for storage in a freezer refer to the WHO  
1401 stability guideline in WHO Technical Report Series, No. 953, Annex 2. APIs intended for  
1402 storage below –20°C should be treated on a case-by-case basis.

1403

1404 To establish the re-test period, data should be provided on not less than three batches of at  
1405 least pilot scale. The batches should be manufactured by the same synthesis route as  
1406 production batches and using a method of manufacture and procedure that simulates the final  
1407 process to be used for production batches. The stability testing programme should be  
1408 summarized and the results of stability testing should be summarized in the dossier and in the  
1409 tables in the QOS-PD.

1410

1411 The information on the stability studies should include details such as storage conditions,  
1412 batch number, batch size, container-closure system and completed (and proposed) test  
1413 intervals. The discussion of results should focus on observations noted for the various tests,  
1414 rather than reporting comments such as “all tests meet specifications”. Ranges of analytical  
1415 results where relevant and any trends that were observed should be included. For quantitative  
1416 tests (e.g. individual and total degradation product tests and assay tests), it should be ensured  
1417 that actual numerical results are provided rather than vague statements such as “within limits”  
1418 or “conforms”. Where different from the methods described in S.4.2, descriptions and  
1419 validation of the methodology used in stability studies should be provided.

1420  
1421  
1422

The minimum data required at the time of submitting the dossier (in the general case):

Storage temperature (°C)	Relative humidity (%)	Minimum time period (months)
Accelerated 40±2	75±5	6
Intermediate *	*	*
Long-term 30±2	65±5 or 75±5	6

1423  
1424  
1425

\*Where long-term conditions are 30 °C±2°C/65%±5%RH or 30 °C±2°C/75%±5%RH, there is no intermediate condition.

1426  
1427  
1428

Refer to WHO Technical Report Series, No. 953, Annex 2 for further information regarding the storage conditions, container-closure system, test specifications and testing frequency.

1429  
1430

*Proposed storage statement and re-test period*

1431  
1432  
1433

A storage statement should be established for display on the label based on the stability evaluation of the API. The WHO stability guideline includes a number of recommended storage statements that should be used, when supported by the stability studies.

1434  
1435  
1436

A re-test period should be derived from the stability information and should be displayed on the container label.

1437  
1438  
1439

After this re-test period, a batch of API destined for use in the manufacture of an FPP could be re-tested and then, if in compliance with the specification, could be used immediately (e.g. within 30 days). If re-tested and found compliant, the batch does *not* receive an additional period corresponding to the time established for the re-test period. However, an API batch can be re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification. For APIs known to be labile (e.g. certain antibiotics), it is more appropriate to establish a shelf-life rather than a re-test period (reference: ICH Q1A).

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1441  
1442

1443  
1444  
1445

1446  
1447  
1448

Limited extrapolation of the real-time data from the long-term storage condition beyond the observed range to extend the re-test period can be undertaken at the time of assessment of the PD, if justified. Applicants should consult the ICH Q1E guideline for further details on the evaluation and extrapolation of results from stability data (e.g. if significant change was not observed within six months at accelerated condition and the data show little or no variability, the proposed re-test period could be up to two times the period covered by the long-term data, but should not exceed the long-term data by 12 months).

1454  
1455  
1456

Reference documents: ICH Q1A, Q1B, Q1D, Q1E, WHO Technical Report Series, No. 953, Annex 2

1457  
1458  
1459

**3.2.S.7.2 Post-approval stability protocol and stability commitment (name, manufacturer)**

1460  
1461

**The post-approval stability protocol and stability commitment should be provided.**

1462  
1463

*Primary stability study commitment*

1464  
1465

When available long-term stability data on primary batches do not cover the proposed re-test period granted at the time of assessment of the PD, a commitment should be made to continue

1466 the stability studies in order to firmly establish the re-test period. A written commitment  
1467 (signed and dated) to continue long-term testing over the re-test period should be included in  
1468 the dossier when relevant.

1469  
1470 *Commitment stability studies*

1471  
1472 The long-term stability studies for the *commitment batches* should be conducted through the  
1473 proposed re-test period on at least three production batches. Where stability data were not  
1474 provided for three production batches, a written commitment (signed and dated) should be  
1475 included in the dossier.

1476  
1477 The stability protocol for the *commitment batches* should be provided and should include, but  
1478 not be limited to, the following parameters:

- 1479 • number of batch(es) and different batch sizes, if applicable;
- 1480 • relevant physical, chemical, microbiological and biological test methods;
- 1481 • acceptance criteria;
- 1482 • reference to test methods;
- 1483 • description of the container-closure system(s);
- 1484 • testing frequency;
- 1485 • description of the conditions of storage (standardized conditions for long-term testing  
1486 as described in these guidelines and consistent with the API labelling, should be used);  
1487 and
- 1488 • other applicable parameters specific to the API.

1489  
1490 *Ongoing stability studies*

1491  
1492 The stability of the API should be monitored according to a continuous and appropriate  
1493 programme that will permit the detection of any stability issue (e.g. changes in levels of  
1494 degradation products). The purpose of the ongoing stability programme is to monitor the API  
1495 and to determine that the API remains and can be expected to remain within the re-test period  
1496 in all future batches.

1497  
1498 At least one production batch per year of API (unless none is produced during that year)  
1499 should be added to the stability monitoring programme and tested at least annually to confirm  
1500 stability. In certain situations, additional batches should be included. A written commitment  
1501 (signed and dated) for ongoing stability studies should be included in the dossier.

1502  
1503 Refer to WHO Technical Report Series, No. 953, Annex 2, section 2.1.11 for further  
1504 information on ongoing stability studies.

1505  
1506 Any differences in the stability protocols used for the primary batches and those proposed for  
1507 the *commitment batches* or *ongoing batches* should be scientifically justified.

1508  
1509 Reference documents: ICH Q1A, Q1B, Q1D, Q1E, WHO Technical Report Series, No. 953,  
1510 Annex 2

1511  
1512 **3.2.S.7.3 Stability data (name, manufacturer)**

1513  
1514 **Results of the stability studies (e.g. forced degradation studies and stress conditions)**  
1515 **should be presented in an appropriate format such as tabular, graphical or narrative.**

1516 **Information on the analytical procedures used to generate the data and validation of**  
1517 **these procedures should be included.**  
1518

1519 The actual stability results used to support the proposed re-test period should be included in  
1520 the dossier. For quantitative tests (e.g. individual and total degradation product tests and assay  
1521 tests) it should be ensured that actual numerical results are provided rather than vague  
1522 statements such as “within limits” or “conforms”.

1523  
1524 Reference documents: ICH Q1A, Q1B, Q1D, Q1E, Q2, WHO Technical Report Series, No.  
1525 953, Annex 2  
1526

### 1527 **3.2.P Drug product (or finished pharmaceutical product (FPP)) (name, dosage form)**

1528

#### 1529 **3.2.P.1 Description and Composition of the FPP (name, dosage form)**

1530

1531 **A description of the FPP and its composition should be provided. The information**  
1532 **provided should include, for example:**

- 1533 • **description of the dosage form**

1534

1535 The description of the FPP should include the physical description, available strengths,  
1536 release mechanism (e.g. immediate, modified (delayed or extended)), as well as any  
1537 other distinguishable characteristics, e.g.

1538 “The proposed XYZ 50mg Tablets are available as white, oval, film-coated tablets,  
1539 debossed with ‘50’ on one side and a break-line on the other side.

1540 The proposed XYZ 100mg Tablets are available as yellow, round, film-coated tablets,  
1541 debossed with ‘100’ on one side and plain on the other side.”

- 1542 • **composition, i.e. list of all components of the dosage form, and their amount on a**  
1543 **per unit basis (including overages, if any), the function of the components, and a**  
1544 **reference to their quality standards (e.g. compendial monographs or**  
1545 **manufacturer’s specifications).**

1546

1547 The tables in the QOS-PD template should be used to summarize the composition of  
1548 the FPP and express the quantity of each component on a per unit basis (e.g. mg per  
1549 tablet, mg per ml, mg per vial) and percentage basis, including a statement of the total  
1550 weight or measure of the dosage unit. The individual components for mixtures  
1551 prepared in-house (e.g. coatings) should be included in the tables, where applicable.

1552

1553 *All components* used in the manufacturing process should be included, including those  
1554 that may not be added to every batch (e.g. acid and alkali), those that may be removed  
1555 during processing (e.g. solvents) and any others (e.g. nitrogen, silicon for stoppers). If  
1556 the FPP is formulated using an active moiety, then the composition for the active  
1557 ingredient should be clearly indicated (e.g. “1 mg of active ingredient base = 1.075 mg  
1558 active ingredient hydrochloride”). All overages should be clearly indicated (e.g.  
1559 “contains 2% overage of the API to compensate for manufacturing losses”).

1560

1561 The components should be declared by their proper or common names, quality  
1562 standards (e.g. BP, JP, Ph.Eur, Ph.Int., USP, house) and, if applicable, their grades

1563 (e.g. “Microcrystalline Cellulose NF (PH 102)”) and special technical characteristics  
1564 (e.g. lyophilized, micronized, solubilized, emulsified).

1565  
1566 The function of each component (e.g. diluent/filler, binder, disintegrant, lubricant,  
1567 glidant, granulating solvent, coating agent, antimicrobial preservative) should be  
1568 stated. If an excipient performs multiple functions, the predominant function should be  
1569 indicated.

1570  
1571 The qualitative composition, including solvents, should be provided for all proprietary  
1572 components or blends (e.g. capsule shells, colouring blends, imprinting inks). This  
1573 information (excluding the solvents) is to be listed in the product information (e.g.  
1574 summary of product characteristics, labelling, package leaflet).

1575  
1576 • **Description of accompanying reconstitution diluent(s)**

1577  
1578 For FPPs supplied with reconstitution diluent(s) that are commercially available or  
1579 have been assessed and considered acceptable in connection with another PD with the  
1580 WHO Prequalification Programme, a brief description of the reconstitution diluents(s)  
1581 should be provided.

1582  
1583 For FPPs supplied with reconstitution diluent(s) that are not commercially available or  
1584 have not been assessed and considered acceptable in connection with another PD with  
1585 the WHO Prequalification Programme, information on the diluent(s) should be  
1586 provided in a separate FPP portion (“3.2.P”), as appropriate.

1587  
1588 • **Type of container and closure used for the dosage form and accompanying**  
1589 **reconstitution diluent, if applicable**

1590  
1591 The container-closure used for the FPP (and accompanying reconstitution diluent, if  
1592 applicable) should be briefly described, with further details provided under 3.2.P.7  
1593 Container-closure system, e.g.

1594  
1595 “The product is available in HDPE bottles with polypropylene caps (in sizes of  
1596 100s, 500s and 1000s) and in PVC/Aluminum foil unit dose blisters (in  
1597 packages of 100s (cards of 5x2, 10 cards per package).”

1598  
1599 Reference documents: ICH Q6A

1600  
1601 **3.2.P.2 Pharmaceutical development (name, dosage form)**

1602  
1603 **The Pharmaceutical development section should contain information on the**  
1604 **development studies conducted to establish that the dosage form, the formulation,**  
1605 **manufacturing process, container-closure system, microbiological attributes and usage**  
1606 **instructions are appropriate for the purpose specified in the product dossier. The studies**  
1607 **described here are distinguished from routine control tests conducted according to**  
1608 **specifications. Additionally, this section should identify and describe the formulation**  
1609 **and process attributes (critical parameters) that can influence batch reproducibility,**  
1610 **product performance and FPP quality. Supportive data and results from specific studies**  
1611 **or published literature can be included within or attached to the Pharmaceutical**  
1612 **development section. Additional supportive data can be referenced to the relevant**  
1613 **nonclinical or clinical sections of the product dossier.**

1614

1615 Pharmaceutical development information should include, at a minimum:

- 1616
- 1617 • the definition of the quality target product profile (QTPP) as it relates to quality, safety  
1618 and efficacy, considering for example the route of administration, dosage form,  
1619 bioavailability, strength and stability;
  - 1620 • identification of the potential critical quality attributes (CQAs) of the FPP so as to  
1621 adequately control the product characteristics that could have an impact on quality;
  - 1622 • discussion of the potential CQAs of the API(s), excipients and container-closure  
1623 system(s) including the selection of the type, grade and amount to deliver drug product  
1624 of the desired quality; and
  - 1625 • discussion of the selection criteria for the manufacturing process and the control  
1626 strategy required to manufacture commercial lots meeting the QTPP in a consistent  
1627 manner.

1628 These features should be discussed as part of the product development using the  
1629 principles of risk management over the entire life-cycle of the product (reference::  
1630 ICH Q8).

1631 For a discussion of additional pharmaceutical development issues specific to the development  
1632 of FDCs, reference should be made to WHO Technical Report Series, No. 929, Annex 5,  
1633 section 6.3.2.

1634

1635 Reference documents: ICH Q6A, Q8, Q9, Q10

1636

### 1637 **3.2.P.2.1 Components of the FPP (name, dosage form)**

1638

#### 1639 **3.2.P.2.1.1 Active pharmaceutical ingredient (name, dosage form)**

1640

1641 **The compatibility of the API with excipients listed in 3.2.P.1 should be discussed.**  
1642 **Additionally, key physicochemical characteristics (e.g. water content, solubility,**  
1643 **particle size distribution, polymorphic or solid state form) of the API that can**  
1644 **influence the performance of the FPP should be discussed. For fixed-dose**  
1645 **combinations, the compatibility of APIs with each other should be discussed.**

1646

1647 Physicochemical characteristics of the API may influence both the manufacturing  
1648 capability and the performance of the FPP.

1649

1650 Guidance on compatibility studies is provided in Appendix 3 of the WHO *Guidelines*  
1651 *for registration of fixed-dose combination medicinal products* (WHO Technical  
1652 Report Series, No. 929, Annex 5, 2005). In addition to visual examination,  
1653 chromatographic results (assay, purity) are required to demonstrate API-API and  
1654 API-excipient compatibility. In general, API-excipient compatibility is not required  
1655 to be established for specific excipients when evidence is provided (e.g. SmPC or  
1656 product leaflet) that the excipients are present in the comparator product.

1657

1658

1659 **3.2.P.2.1.2 Excipients (name, dosage form)**

1660

1661 **The choice of excipients listed in 3.2.P.1, their concentration and their**  
1662 **characteristics that can influence the FPP performance should be discussed**  
1663 **relative to their respective functions.**

1664

1665 When choosing excipients, those with a compendial monograph are generally  
1666 preferred and may be required in certain jurisdictions. Other resources are available  
1667 for information on acceptable excipients and their concentrations, such as the US-FDA  
1668 IIG List and the Handbook of Pharmaceutical Excipients. Use of excipients in  
1669 concentrations outside of established ranges are discouraged and generally requires  
1670 justifications. In addition, available guidelines should be referenced which address  
1671 particular excipients to be avoided, for example azo colorants as listed in the EMA  
1672 Guideline CPMP/463/00, and the Colocon Regulatory Information Sheet on Azo and  
1673 non-azo colorants. Other guidance such as the WHO Guideline on development of  
1674 paediatric medicines may provide useful general guidance in this regard.

1675

1676 Ranges or alternates for excipients are normally not accepted, unless supported by  
1677 appropriate process validation data. Where relevant, compatibility study results (e.g.  
1678 compatibility of a primary or secondary amine API with lactose) should be included to  
1679 justify the choice of excipients. Specific details should be provided where necessary  
1680 (e.g. use of potato or corn starch).

1681

1682 Where antioxidants are included in the formulation, the effectiveness of the proposed  
1683 concentration of the antioxidant should be justified and verified by appropriate studies.

1684

1685 Antimicrobial preservatives are discussed in 3.2.P.2.5.

1686

1687 **3.2.P.2.2 Finished pharmaceutical product (name, dosage form)**

1688

1689 **3.2.P.2.2.1 Formulation development (name, dosage form)**

1690

1691 **A brief summary describing the development of the FPP should be provided,**  
1692 **taking into consideration the proposed route of administration and usage. The**  
1693 **differences between the comparative bioavailability or biowaiver formulations**  
1694 **and the formulation (i.e. composition) described in 3.2.P.1 should be discussed.**  
1695 **Results from comparative in vitro studies (e.g. dissolution) or comparative in vivo**  
1696 **studies (e.g. bioequivalence) should be discussed when appropriate.**

1697

1698 The Prequalification Programme defines an *established multisource product* as one  
1699 that has been marketed by the applicant or manufacturer associated with the dossier  
1700 for at least five years and for which at least 10 production batches were produced over  
1701 the previous year or, if less than 10 batches were produced in the previous year, not  
1702 less than 25 batches were produced in the previous three years. For products that meet  
1703 the criteria of an *established multisource product* all sections of P.2.2.1 of the dossier  
1704 and QOS-PD should be completed, with the exception of P.2.2.1 (a). In addition, a  
1705 product quality review should be provided as outlined in Appendix 2.

1706

1707 The requirements for bioequivalence studies should be taken into consideration, for  
1708 example, when formulating multiple strengths and/or when the product(s) may be

1709 eligible for a biowaiver. WHO reference documents (e.g. WHO Technical Report  
1710 Series, No. 937, Annex 7) should be consulted.

1711  
1712 Product scoring may be recommended or required, for example, when scoring is  
1713 indicated in the WHO invitation for EOI, or is specified for an invited FPP in the  
1714 listing of recommended comparator products, or when division into fractional doses  
1715 may be necessary according to approved posology.

1716  
1717 If the proposed FPP is a functionally scored tablet, a study should be undertaken to  
1718 ensure the uniformity of dose in the tablet fragments. The data provided in the PD  
1719 should include a description of the test method, individual values, mean and relative  
1720 standard deviation (RSD) of the results. Uniformity testing (i.e. content uniformity or  
1721 mass variation, depending on the requirement for the whole tablet) should be  
1722 performed on each split portion from a minimum of 10 randomly selected whole  
1723 tablets. As an illustrative example, the number of units (i.e. the splits) would be 10  
1724 halves for bisected tablets (one half of each tablet is retained for the test) or 10  
1725 quarters for quadrisectioned tablets (one quarter of each tablet is retained for the test). At  
1726 least one batch of each strength should be tested. Ideally, the study should cover a  
1727 range of the hardness values. The splitting of the tablets should be performed in a  
1728 manner that would be representative of that used by the consumer (e.g. manually split  
1729 by hand). The uniformity test on split portions can be demonstrated on a one-time  
1730 basis and does not need to be added to the FPP specification(s). The tablet description  
1731 in the FPP specification and in the product information (e.g. summary of product  
1732 characteristics, labelling, package leaflet) should reflect the presence of a score.

1733  
1734 If splitting of a tablet is intended for a paediatric dose, a demonstration of content  
1735 uniformity of tablet fragments may be required.

1736  
1737 Where relevant, labelling should state that the score line is only to facilitate breaking  
1738 for ease of swallowing and not to divide into equal doses. *In vitro dissolution or drug  
1739 release.*

1740  
1741 A discussion should be included as to how the development of the formulation relates  
1742 to development of the dissolution method(s) and the generation of the dissolution  
1743 profile.

1744  
1745 The results of studies justifying the choice of *in vitro* dissolution or drug release  
1746 conditions (e.g. apparatus, rotation speed, medium) should be provided. Data should  
1747 also be submitted to demonstrate whether the method is sensitive to changes in  
1748 manufacturing processes and/or changes in grades and/or amounts of critical  
1749 excipients and particle size where relevant. The dissolution method should be sensitive  
1750 to any changes in the product that would result in a change in one or more of the  
1751 pharmacokinetic parameters. Use of a single point test or a dissolution range should be  
1752 justified based on the solubility and/or biopharmaceutical classification of the API.

1753  
1754 For slower dissolving immediate-release products (e.g. Q=80% in 90 minutes), a  
1755 second time point may be warranted (e.g. Q=60% in 45 minutes).

1756  
1757 Modified-release FPPs should have a meaningful *in vitro* release rate (dissolution) test  
1758 that is used for routine quality control. Preferably this test should possess *in vitro*-in

1759 vivo correlation. Results demonstrating the effect of pH on the dissolution profile  
1760 should be submitted if appropriate for the type of dosage form.  
1761

1762 For extended-release FPPs, the testing conditions should be set to cover the entire time  
1763 period of expected release (e.g. at least three test intervals chosen for a 12-hour release  
1764 and additional test intervals for longer duration of release). One of the test points  
1765 should be at the early stage of drug release (e.g. within the first hour) to demonstrate  
1766 absence of dose dumping. At each test period, upper and lower limits should be set for  
1767 individual units. Generally, the acceptance range at each intermediate test point should  
1768 not exceed 25% or  $\pm 12.5\%$  of the targeted value. Dissolution results should be  
1769 submitted for several lots, including those lots used for pharmacokinetic and  
1770 bioavailability or biowaiver studies.  
1771

1772 Recommendations for conducting and assessing comparative dissolution profiles can  
1773 be found in Appendix 1.  
1774

#### 1775 **3.2.P.2.2.2 Overages (name, dosage form)**

1776 **Any overages in the formulation(s) described in 3.2.P.1 should be justified.**  
1777

1778 Justification of an overage to compensate for loss during manufacture should be  
1779 provided, including the step(s) where the loss occurs, the reasons for the loss and  
1780 batch analysis release data (assay results).  
1781

1782 Overages for the sole purpose of extending the shelf-life of the FPP are generally not  
1783 acceptable.  
1784

#### 1785 **3.2.P.2.2.3 Physicochemical and biological properties (name, dosage form)**

1786 **Parameters relevant to the performance of the FPP, such as pH, ionic strength,**  
1787 **dissolution, redispersion, reconstitution, particle size distribution, aggregation,**  
1788 **polymorphism, rheological properties, biological activity or potency and/or**  
1789 **immunological activity, should be addressed.**  
1790

#### 1791 **3.2.P.2.3 Manufacturing process development (name, dosage form)**

1792 **The selection and optimization of the manufacturing process described in 3.2.P.3.3, in**  
1793 **particular its critical aspects, should be explained. Where relevant, the method of**  
1794 **sterilisation should be explained and justified.**  
1795

1796 Where relevant, justification for the selection of aseptic processing or other sterilization  
1797 methods over terminal sterilization should be provided.  
1798

1799 **Differences between the manufacturing process(es) used to produce comparative**  
1800 **bioavailability or biowaiver batches and the process described in 3.2.P.3.3 that can**  
1801 **influence the performance of the product should be discussed.**  
1802

1803 For products that meet the criteria of an *established multisource product*, in order to fulfil the  
1804 requirements of section P.2.3, section P.2.3 (b) of the dossier and QOS-PD should be  
1805 completed and a product quality review should be submitted as outlined in Appendix 2. The  
1806

1810 guidance that follows applies to all other products, for which section P.2.3 should be  
1811 completed in its entirety.

1812  
1813 The rationale for choosing the particular pharmaceutical product (e.g. dosage form, delivery  
1814 system) should be provided. The scientific rationale for the choice of the manufacturing,  
1815 filling and packaging processes that can influence FPP quality and performance should be  
1816 explained (e.g. wet granulation using high shear granulator). API stress study results may be  
1817 included in the rationale. Any developmental work undertaken to protect the FPP from  
1818 deterioration should also be included (e.g. protection from light or moisture).

1819  
1820 The scientific rationale for the selection, optimization and scale-up of the manufacturing  
1821 process described in 3.2.P.3.3 should be explained, in particular the critical aspects (e.g. rate  
1822 of addition of granulating fluid, massing time, granulation end-point). A discussion of the  
1823 critical process parameters (CPP), controls and robustness with respect to the QTPP and CQA  
1824 of the product should be included (reference: ICH Q8).

1825  
1826 **3.2.P.2.4 Container-closure system (name, dosage form)**

1827  
1828 **The suitability of the container-closure system (described in 3.2.P.7) used for the**  
1829 **storage, transportation (shipping) and use of the FPP should be discussed. This**  
1830 **discussion should consider, e.g. choice of materials, protection from moisture and light,**  
1831 **compatibility of the materials of construction with the dosage form (including sorption**  
1832 **to container and leaching) safety of materials of construction and performance (such as**  
1833 **reproducibility of the dose delivery from the device when presented as part of the FPP).**

1834  
1835 Testing requirements to verify the suitability of the container-closure system contact  
1836 material(s) depend on the dosage form and route of administration. The pharmacopoeias  
1837 provide standards that are required for packaging materials, including, for example, the  
1838 following:

1839	Glass containers:	USP <660>
1840		PhEur 3.2.1
1841	Plastic containers:	PhEur 3.2.2, 3.2.2.1
1842		USP <661>
1843	Rubber/Elastomeric closures:	USP <381>
1844		PhEur 3.2.9

1845  
1846 The following table outlines the general recommendations for the various dosage forms for  
1847 one-time studies to establish the suitability of the container-closure system contact materials.

1848  
1849

	<b>Solid oral products</b>	<b>Oral liquid and topical products</b>	<b>Sterile products (including ophthalmics)</b>
Description of any additional treatments*	X	X	X (sterilization and depyrogenation of the components)
Extraction studies	---	X	X
Interaction studies (Migration/Sorption)	---	X	X
Moisture permeability	X (uptake)	X (usually loss)	X (usually loss)
Light transmission	X**	X	X

1850 \*e.g. coating of tubes, siliconization of rubber stoppers, sulfur treatment of ampoules/vials

1851 X = information should be submitted

1852 --- = information does not need to be submitted

1853 \*\*Not required if product has been shown to be photostable

1854

1855 The suitability of the container-closure system used for the storage, transportation (shipping)  
1856 and use of any intermediate/in-process products (e.g. premixes, bulk FPP) should also be  
1857 discussed.

1858

1859 A device is required to be included with the container-closure system for oral liquids or solids  
1860 (e.g. solutions, emulsions, suspensions and powders/granules for such), any time the package  
1861 provides for multiple doses.

1862

1863 In accordance with the Ph.Int. general chapter *Liquid Preparations for Oral Use*:

1864 *“Each dose from a multidose container is administered by means of a device suitable*  
1865 *for measuring the prescribed volume. The device is usually a spoon or a cup for*  
1866 *volumes of 5 ml or multiples thereof, or an oral syringe for other volumes or, for oral*  
1867 *drops, a suitable dropper.”*

1868

1869 For a device accompanying a multidose container, the results of a study should be provided  
1870 demonstrating the reproducibility of the device (e.g. consistent delivery of the intended  
1871 volume), generally at the lowest intended dose.

1872

1873 A sample of the device should be provided with *Module 1*.

1874

1875 **3.2.P.2.5 Microbiological attributes (name, dosage form)**

1876

1877 **Where appropriate the microbiological attributes of the dosage form should be**  
1878 **discussed, including, for example, the rationale for not performing microbial limits**  
1879 **testing for non-sterile products and the selection and effectiveness of preservative**  
1880 **systems in products containing antimicrobial preservatives. For sterile products the**  
1881 **integrity of the container-closure system to prevent microbial contamination should be**  
1882 **addressed.**

1883

1884 Where an antimicrobial preservative is included in the formulation, the amount used should  
1885 be justified by submission of results of the product formulated with different concentrations of

1886 the preservative(s) to demonstrate the least necessary but still effective concentration. The  
1887 effectiveness of the agent should be justified and verified by appropriate studies (e.g. USP or  
1888 PhEur general chapters on antimicrobial preservatives) using a batch of the FPP. If the lower  
1889 bound limit for the proposed acceptance criterion for the assay of the preservative is less than  
1890 90.0%, the effectiveness of the agent should be established with a batch of the FPP containing  
1891 a concentration of the antimicrobial preservative corresponding to the lower proposed  
1892 acceptance criteria.

1893  
1894 As outlined in the WHO stability guideline (WHO Technical Report Series, No. 953, Annex  
1895 2, 2009), a single primary stability batch of the FPP should be tested for effectiveness of the  
1896 antimicrobial preservative (in addition to preservative content) at the proposed shelf-life for  
1897 verification purposes, regardless of whether there is a difference between the release and  
1898 shelf-life acceptance criteria for preservative content.

### 1899 1900 **3.2.P.2.6 Compatibility (name, dosage form)**

1901  
1902 **The compatibility of the FPP with reconstitution diluent(s) or dosage devices (e.g.**  
1903 **precipitation of API in solution, sorption on injection vessels, stability) should be**  
1904 **addressed to provide appropriate and supportive information for the labelling.**

1905  
1906 Where a device is required for oral liquids or solids (e.g. solutions, emulsions, suspensions  
1907 and powders/granules for such reconstitution) that are intended to be administered  
1908 immediately after being added to the device, the compatibility studies mentioned in the  
1909 following paragraphs are not required.

1910  
1911 Where sterile, reconstituted products are to be further diluted, compatibility should be  
1912 demonstrated with all diluents over the range of dilution proposed in the labelling. These  
1913 studies should preferably be conducted on aged samples. Where the labelling does not specify  
1914 the type of containers, compatibility (with respect to parameters such as appearance, pH,  
1915 assay, levels of individual and total degradation products, subvisible particulate matter and  
1916 extractables from the packaging components) should be demonstrated in glass, PVC and  
1917 polyolefin containers. However, if one or more containers are identified in the labelling,  
1918 compatibility of admixtures needs to be demonstrated only in the specified containers.

1919  
1920 Studies should cover the duration of storage reported in the labelling (e.g. 24 hours under  
1921 controlled room temperature and 72 hours under refrigeration). Where the labelling specifies  
1922 coadministration with other FPPs, compatibility should be demonstrated with respect to the  
1923 principal FPP as well as the coadministered FPP (i.e. in addition to other aforementioned  
1924 parameters for the mixture, the assay and degradation levels of each coadministered FPP  
1925 should be reported).

### 1926 1927 **3.2.P.3 Manufacture (name, dosage form)**

#### 1928 1929 **3.2.P.3.1 Manufacturer(s) (name, dosage form)**

1930  
1931 **The name, address and responsibility of each manufacturer, including contractors, and**  
1932 **each proposed production site or facility involved in manufacturing and testing should**  
1933 **be provided.**

1934  
1935 The facilities involved in the manufacturing, packaging, labelling and testing should be listed.  
1936 If certain companies are responsible only for specific steps (e.g. manufacturing of an

1937 intermediate), this should be clearly indicated (reference: WHO good distribution practices  
1938 for pharmaceutical products, WHO Technical Report Series, No. 957, Annex 5).

1939  
1940 The list of manufacturers/companies should specify the *actual addresses* of production or  
1941 manufacturing site(s) involved (including block(s) and unit(s)), rather than the administrative  
1942 offices.

1943  
1944 For a mixture of an API with an excipient, the blending of the API with the excipient is  
1945 considered to be the first step in the manufacture of the final product and, therefore, the  
1946 mixture does not fall under the definition of an API. The only exceptions are in the cases  
1947 where the API cannot exist on its own. Similarly, for a mixture of APIs, the blending of the  
1948 APIs is considered to be the first step in the manufacture of the final product. Sites for such  
1949 manufacturing steps should be included in this section.

1950  
1951 A valid manufacturing authorization for pharmaceutical production, as well as  
1952 a marketing authorization, should be submitted to demonstrate that the product is registered or  
1953 licensed in accordance with national requirements (*Module 1*, 1.2.2).

1954  
1955 For each site where the major production step(s) are carried out, when applicable attach a  
1956 WHO-type certificate of GMP issued by the competent authority in terms of the WHO  
1957 Certification Scheme on the quality of pharmaceutical products moving in international  
1958 commerce (*Module 1*, 1.2.2).

1959  
1960 *Justification for any differences to the product in the country or countries issuing the WHO-*  
1961 *type certificate(s)*

1962  
1963 When there are differences between the product for which this application is submitted and  
1964 that marketed in the country/countries which provided the WHO-type certificate(s), provide  
1965 data to support the applicability of the certificate(s) despite the differences. Depending on the  
1966 case, it may be necessary to provide validation data for differences in site of manufacture,  
1967 specifications, formulation, etc. Note that only minor differences are likely to be acceptable.  
1968 Differences in container labelling need not normally be justified.

1969  
1970 *Regulatory situation in other countries*

1971  
1972 The countries should be listed in which this product has been granted a marketing  
1973 authorization, this product has been withdrawn from the market and/or this application for  
1974 marketing has been rejected, deferred or withdrawn (*Module 1*, 1.2.2).

1975  
1976 Reference documents: WHO Technical Report Series, No. 908, Annex 4 and No. 957, Annex 5  
1977

1978 **3.2.P.3.2 Batch formula (name, dosage form)**

1979  
1980 **A batch formula should be provided that includes a list of all components of the dosage**  
1981 **form to be used in the manufacturing process, their amounts on a per batch basis,**  
1982 **including overages, and a reference to their quality standards.**

1983  
1984 The tables in the QOS-PD template should be used to summarize the batch formula of the  
1985 FPP for each proposed commercial batch size and express the quantity of each component on  
1986 a per batch basis, including a statement of the total weight or measure of the batch.

1987

1988 All components used in the manufacturing process should be included, including those that  
1989 may not be added to every batch (e.g. acid and alkali), those that may be removed during  
1990 processing (e.g. solvents) and any others (e.g. nitrogen, silicon for stoppers). If the FPP is  
1991 formulated using an active moiety, then the composition for the active ingredient should be  
1992 clearly indicated (e.g. “1 kg of active ingredient base = 1.075 kg active ingredient  
1993 hydrochloride”). All overages should be clearly indicated (e.g. “Contains 5 kg (corresponding  
1994 to 2%) overage of the API to compensate for manufacturing losses”).  
1995

1996 The components should be declared by their proper or common names, quality standards (e.g.  
1997 BP, JP, Ph.Eur, Ph.Int., USP, house) and, if applicable, their grades (e.g. “Microcrystalline  
1998 Cellulose NF (PH 102)”) and special technical characteristics (e.g. lyophilized, micronized,  
1999 solubilized, emulsified).  
2000

### 2001 **3.2.P.3.3 Description of manufacturing process and process controls (name, dosage form)**

2002

2003 **A flow diagram should be presented giving the steps of the process and showing where**  
2004 **materials enter the process. The critical steps and points at which process controls,**  
2005 **intermediate tests or final product controls are conducted should be identified.**  
2006

2007 **A narrative description of the manufacturing process, including packaging, that**  
2008 **represents the sequence of steps undertaken and the scale of production should also be**  
2009 **provided. Novel processes or technologies and packaging operations that directly affect**  
2010 **product quality should be described with a greater level of detail. Equipment should, at**  
2011 **least, be identified by type (e.g. tumble blender, in-line homogenizer) and working**  
2012 **capacity, where relevant.**  
2013

2014 **Steps in the process should have the appropriate process parameters identified, such as**  
2015 **time, temperature or pH. Associated numeric values can be presented as an expected**  
2016 **range. Numeric ranges for critical steps should be justified in section 3.2.P.3.4. In**  
2017 **certain cases, environmental conditions (e.g. low humidity for an effervescent product)**  
2018 **should be stated.**  
2019

2020 The maximum holding time for bulk FPP prior to final packaging should be stated. The  
2021 holding time should be supported by the submission of stability data, if longer than 30 days.  
2022 For an aseptic FPP, the holding time of the filtered product prior to filling should be supported  
2023 by the submission of stability data, if longer than 24 hours.  
2024

2025 **Proposals for the reprocessing of materials should be justified. Any data to support this**  
2026 **justification should be either referenced or filed in this section (3.2.P.3.3).**  
2027

2028 The information above should be summarized in the QOS-PD template and should reflect the  
2029 production of the proposed commercial batches. See section 2. *Glossary* for definitions of  
2030 pilot-scale and production-scale batches.  
2031

2032 For the manufacture of sterile products, the class (e.g. A, B, C, etc.) of the areas should be  
2033 stated for each activity (e.g. compounding, filling, sealing, etc.), as well as the sterilization  
2034 parameters for equipment, container/closure, terminal sterilization, etc.  
2035

2036 Reference documents: ICH Q8, Q9, Q10  
2037  
2038

2039 **3.2.P.3.4 Controls of critical steps and intermediates (name, dosage form)**  
2040

2041 **Critical steps: tests and acceptance criteria should be provided (with justification,**  
2042 **including experimental data) performed at the critical steps identified in 3.2.P.3.3 of the**  
2043 **manufacturing process, to ensure that the process is controlled.**  
2044

2045 **Intermediates: information on the quality and control of intermediates isolated during**  
2046 **the process should be provided.**  
2047

2048 Examples of applicable in-process controls include:

- 2049 • granulations: moisture (limits expressed as a range), blend uniformity (e.g. low-dose  
2050 tablets), bulk and tapped densities, particle size distribution;
- 2051 • solid oral products: average weight, weight variation, hardness, thickness, friability  
2052 and disintegration checked periodically throughout compression, weight gain during  
2053 coating;
- 2054 • semisolids: viscosity, homogeneity, pH;
- 2055 • transdermal dosage forms: assay of API-adhesive mixture, weight per area of coated  
2056 patch without backing;
- 2057 • metered dose inhalers: fill weight/volume, leak testing, valve delivery;
- 2058 • dry powder inhalers: assay of API–excipient blend, moisture, weight variation of  
2059 individually contained doses such as capsules or blisters;
- 2060 • liquids: pH, specific gravity, clarity of solutions; and
- 2061 • parenterals: appearance, clarity, fill volume/weight, pH, filter integrity tests,  
2062 particulate matter, leak testing of ampoules.

2063  
2064 Reference documents: ICH Q2, Q6A, Q8, Q9, Q10, WHO Technical Report Series, No. 929,  
2065 Annex 5  
2066

2067 **3.2.P.3.5 Process validation and/or evaluation (name, dosage form)**  
2068

2069 **Description, documentation and results of the validation and/or evaluation studies**  
2070 **should be provided for critical steps or critical assays used in the manufacturing process**  
2071 **(e.g. validation of the sterilization process or aseptic processing or filling). Viral safety**  
2072 **evaluation should be provided in 3.2.A.2 if necessary.**  
2073

2074 For products that meet the criteria of an *established multisource product*, a product quality  
2075 review as outlined in Appendix 2 may be submitted in lieu of the information below.  
2076

2077 The following information should be provided for all other products:

- 2078 a) a copy of the *process validation protocol*, specific to this FPP, that identifies the  
2079 critical equipment and process parameters that can affect the quality of the FPP and  
2080 defines testing parameters, sampling plans, analytical procedures and acceptance  
2081 criteria;
- 2082 b) a *commitment* that three consecutive, production-scale batches of this FPP will be  
2083 subjected to *prospective validation* in accordance with the above protocol. The  
2084 applicant should submit a written commitment that information from these studies will  
2085 be available for verification after prequalification by the WHO inspection team; and

2086 c) if the process validation studies have already been conducted (e.g. for sterile  
2087 products), a copy of the *process validation report* should be provided in the PD in lieu  
2088 of (a) and (b) above.  
2089

2090 One of the most practical forms of process validation, mainly for non-sterile products, is the  
2091 final testing of the product to an extent greater than that required in routine quality control. It  
2092 may involve extensive sampling, far beyond that called for in routine quality control and  
2093 testing to normal quality control specifications and often for certain parameters only. Thus,  
2094 for instance, several hundred tablets per batch may be weighed to determine unit dose  
2095 uniformity. The results are then treated statistically to verify the "normality" of the  
2096 distribution and to determine the standard deviation from the average weight. Confidence  
2097 limits for individual results and for batch homogeneity are also estimated. Strong assurance is  
2098 provided that samples taken at random will meet regulatory requirements if the confidence  
2099 limits are well within compendial specifications.

2100  
2101 Similarly, extensive sampling and testing may be performed with regard to any quality  
2102 requirements. In addition, intermediate stages may be validated in the same way, e.g. dozens  
2103 of samples may be assayed individually to validate mixing or granulation stages of low-dose  
2104 tablet production by using the content uniformity test. Products (intermediate or final) may  
2105 occasionally be tested for non-routine characteristics. Thus, subvisual particulate matter in  
2106 parenteral preparations may be determined by means of electronic devices, or tablets/capsules  
2107 tested for dissolution profile if such tests are not performed on every batch.  
2108

2109 Where ranges of batch sizes are proposed, it should be shown that variations in batch size  
2110 would not adversely alter the characteristics of the finished product. It is envisaged that those  
2111 parameters listed in the following validation scheme will need to be revalidated once further  
2112 scale-up is proposed after prequalification.  
2113

2114 The process validation protocol should include inter alia the following:

- 2115 – a reference to the current master production document;
- 2116 – a discussion of the critical equipment;
- 2117 – the process parameters that can affect the quality of the FPP (critical process  
2118 parameters (CPPs)) including challenge experiments and failure mode  
2119 operation;
- 2120 – details of the sampling: sampling points, stages of sampling, methods of  
2121 sampling and the sampling plans (including schematics of blender/storage bins  
2122 for uniformity testing of the final blend);
- 2123 – the testing parameters/acceptance criteria including in-process and release  
2124 specifications and including comparative dissolution profiles of validation  
2125 batches against the batch(es) used in the bioavailability or biowaiver studies;
- 2126 – the analytical procedures or a reference to appropriate section(s) of the dossier;
- 2127 – the methods for recording/evaluating results; and
- 2128 – the proposed timeframe for completion of the protocol.

2129  
2130 The manufacture of sterile FPPs needs a well-controlled manufacturing area (e.g. a strictly  
2131 controlled environment, highly reliable procedures and appropriate in-process controls). A  
2132 detailed description of these conditions, procedures and controls should be provided, together  
2133 with actual copies of the following standard operating procedures:

- 2134 a) washing, treatment, sterilizing and depyrogenating of containers, closures and
- 2135 equipment;
- 2136 b) filtration of solutions;
- 2137 c) lyophilization process;
- 2138 d) leaker test of filled and sealed ampoules;
- 2139 e) final inspection of the product; and
- 2140 f) sterilization cycle.

2141

2142 The sterilization process used to destroy or remove microorganisms is probably the single  
2143 most important process in the manufacture of parenteral FPPs. The process can make use of  
2144 moist heat (e.g. steam), dry heat, filtration, gaseous sterilization (e.g. ethylene oxide) or  
2145 radiation. It should be noted that terminal steam sterilization, when practical, is considered to  
2146 be the method of choice to ensure sterility of the final FPP. Therefore, scientific justification  
2147 for selecting any other method of sterilization should be provided.

2148

2149 The sterilization process should be described in detail and evidence should be provided to  
2150 confirm that it will produce a sterile product with a high degree of reliability and that the  
2151 physical and chemical properties as well as the safety of the FPP will not be affected. Details  
2152 such as Fo range, temperature range and peak dwell time for an FPP and the container-closure  
2153 should be provided. Although standard autoclaving cycles of 121 °C for 15 minutes or more  
2154 would not need a detailed rationale, such justifications should be provided for reduced  
2155 temperature cycles or elevated temperature cycles with shortened exposure times. If ethylene  
2156 oxide is used, studies and acceptance criteria should control the levels of residual ethylene  
2157 oxide and related compounds.

2158

2159 Filters used should be validated with respect to pore size, compatibility with the product,  
2160 absence of extractables and lack of adsorption of the API or any of the components.

2161

2162 For the validation of aseptic filling of parenteral products that cannot be terminally sterilized,  
2163 simulation process trials should be conducted. This involves filling ampoules with culture  
2164 media under normal conditions, followed by incubation and control of microbial growth. A  
2165 level of contamination of less than 0.1% is considered to be acceptable.

2166

2167 Reference documents: ICH Q8, Q9, Q10, WHO Technical Report Series, Nos 902 and 908

2168

### 2169 **3.2.P.4 Control of excipients (name, dosage form)**

2170

#### 2171 **3.2.P.4.1 Specifications (name, dosage form)**

2172

#### 2173 **The specifications for excipients should be provided.**

2174

2175 The specifications from the applicant or the FPP manufacturer should be provided for all  
2176 excipients, including those that may not be added to every batch (e.g. acid and alkali), those  
2177 that do not appear in the final FPP (e.g. solvents) and any others used in the manufacturing  
2178 process (e.g. nitrogen, silicon for stoppers).

2179

2180 If the standard claimed for an excipient is an officially recognized compendial standard, it is  
2181 sufficient to state that the excipient is tested according to the requirements of that standard,  
2182 rather than reproducing the specifications found in the officially recognized compendial  
2183 monograph.

2184

2185 If the standard claimed for an excipient is a noncompendial standard (e.g. house standard) or  
2186 includes tests that are supplementary to those appearing in the officially recognized  
2187 compendial monograph, a copy of the specification for the excipient should be provided.  
2188

2189 For products submitted to the Prequalification Programme, only excipients with an officially  
2190 recognized pharmacopoeial monograph should be used.  
2191

2192 For excipients of natural origin, microbial limit testing should be included in the  
2193 specifications. Skip testing is acceptable if justified (submission of acceptable results of five  
2194 production batches).  
2195

2196 For oils of plant origin (e.g. soy bean, peanut) the absence of aflatoxins or biocides should be  
2197 demonstrated.  
2198

2199 The colours permitted for use are limited to those listed in the “Japanese pharmaceutical  
2200 excipients”, the EU “List of permitted food colours”, and the FDA “Inactive ingredient  
2201 guide”. For proprietary mixtures, the supplier’s product sheet with the qualitative formulation  
2202 should be submitted, in addition to the FPP manufacturer’s specifications for the product  
2203 including identification testing.  
2204

2205 For flavours the qualitative composition should be submitted, as well as a declaration that the  
2206 excipients comply with foodstuff regulations (e.g. USA or EU).  
2207

2208 Information that is considered confidential may be submitted directly to the WHO  
2209 Prequalification Programme by the supplier with reference to the specific related product.  
2210

2211 Other certifications of at-risk components may be required on a case-by-case basis.  
2212

2213 If additional purification is undertaken on commercially available excipients details of the  
2214 process of purification and modified specifications should be submitted.  
2215

2216 Reference documents: ICH Q6A  
2217

#### 2218 ***3.2.P.4.2 Analytical procedures (name, dosage form)*** 2219

2220 **The analytical procedures used for testing the excipients should be provided where  
2221 appropriate.**  
2222

2223 Copies of analytical procedures from officially recognized compendial monographs do not  
2224 need to be submitted.  
2225

2226 Reference documents: ICH Q2  
2227

#### 2228 ***3.2.P.4.3 Validation of analytical procedures (name, dosage form)*** 2229

2230 **Analytical validation information, including experimental data, for the analytical  
2231 procedures used for testing the excipients should be provided where appropriate.**  
2232

2233 Copies of analytical validation information are generally not submitted for the testing of  
2234 excipients, with the exception of the validation of in-house methods where appropriate.  
2235

2236 Reference documents: ICH Q2

2237

2238 **3.2.P.4.4 Justification of specifications (name, dosage form)**

2239

2240 **Justification for the proposed excipient specifications should be provided where**  
2241 **appropriate.**

2242

2243 A discussion of the tests that are supplementary to those appearing in the officially recognized  
2244 compendial monograph should be provided.

2245

2246 **3.2.P.4.5 Excipients of human or animal origin (name, dosage form)**

2247

2248 **For excipients of human or animal origin, information should be provided regarding**  
2249 **adventitious agents (e.g. sources, specifications, description of the testing performed,**  
2250 **viral safety data – details in 3.2.A.2).**

2251

2252 The following excipients should be addressed in this section: gelatin, phosphates, stearic acid,  
2253 magnesium stearate and other stearates. If from plant origin a declaration to this effect will  
2254 suffice.

2255 For these excipients from animal origin, a letter of attestation should be provided confirming  
2256 that the excipients used to manufacture the FPP are *without* risk of transmitting agents of  
2257 animal spongiform encephalopathies.

2258

2259 Materials of animal origin should be avoided whenever possible.

2260

2261 When available, a CEP demonstrating TSE-compliance should be provided. A complete copy  
2262 of the CEP (including any annexes) should be provided in Module 1.

2263

2264 Reference documents: ICH Q5A, Q5D, Q6B, WHO Technical Report Series, No. 908, Annex 1

2265

2266 **3.2.P.4.6 Novel excipients (name, dosage form)**

2267

2268 **For excipient(s) used for the first time in an FPP or by a new route of administration,**  
2269 **full details of manufacture, characterization and controls, with cross references to**  
2270 **supporting safety data (nonclinical and/or clinical), should be provided according to the**  
2271 **API and/or FPP format (details in 3.2.A.3).**

2272

2273 Novel excipients are not accepted in the Prequalification Programme.

2274

2275 **3.2.P.5 Control of FPP (name, dosage form)**

2276

2277 **3.2.P.5.1 Specification(s) (name, dosage form)**

2278

2279 **The specification(s) for the FPP should be provided.**

2280

2281 As defined in ICH's Q6A guideline, a specification is:

2282

2283 *“A list of tests, references to analytical procedures and appropriate acceptance*  
2284 *criteria, which are numerical limits, ranges, or other criteria for the tests described. It*  
2285 *establishes the set of criteria to which an API or FPP should conform to be*  
*considered acceptable for its intended use. 'Conformance to specifications' means that*

2286 *the API and / or FPP, when tested according to the listed analytical procedures, will*  
2287 *meet the listed acceptance criteria. Specifications are critical quality standards that*  
2288 *are proposed and justified by the manufacturer and approved by regulatory*  
2289 *authorities.”*  
2290

2291 A copy of the FPP specification(s) from the applicant (as well as the company responsible for  
2292 the batch release of the FPP, if different from the applicant), dated and signed by the  
2293 authorized personnel (i.e. the person in charge of the quality control or quality assurance  
2294 department) should be provided in the PD. Two separate sets of specifications may be set out:  
2295 after packaging of the FPP (release) and at the end of the shelf-life.  
2296

2297 The specifications should be summarized according to the tables in the QOS-PD template  
2298 including the tests, acceptance criteria and analytical procedures (including types, sources and  
2299 versions for the methods):

- 2300 • the *standard* declared by the applicant could be an officially recognized compendial  
2301 standard (e.g. BP, JP, Ph.Eur, Ph.Int., USP) or a house standard;
- 2302 • the *specification reference number and version* (e.g. *revision number and/or date*)  
2303 should be provided for version control purposes; and
- 2304 • for the analytical procedures, the *type* should indicate the kind of analytical procedure  
2305 used (e.g. visual, IR, UV, HPLC), the *source* refers to the origin of the analytical  
2306 procedure (e.g. BP, JP, Ph.Eur, Ph.Int., USP, in-house) and the *version* (e.g. *code*  
2307 *number/version/date*) should be provided for version control purposes.  
2308

2309 ICH's Q6A guideline outlines recommendations for a number of *universal* and *specific tests*  
2310 and criteria for FPPs. Specifications should include, at minimum, tests for appearance,  
2311 identification, assay, purity, pharmaceutical tests (e.g. dissolution), physical tests (e.g. loss on  
2312 drying, hardness, friability, particle size, apparent density), uniformity of dosage units,  
2313 identification of colouring materials, identification and assay of antimicrobial or chemical  
2314 preservatives (e.g. antioxidants) and microbial limit tests.  
2315

2316 The following information provides guidance for specific tests that are not addressed by  
2317 ICH's Q6A guideline:

- 2318 • fixed-dose combination FPPs (FDC-FPPs):
  - 2319 ○ analytical methods that can distinguish each API in the presence of the other  
2320 API(s) should be developed and validated,
  - 2321 ○ acceptance criteria for degradation products should be established with  
2322 reference to the API they are derived from. If an impurity results from a  
2323 chemical reaction between two or more APIs, its acceptance limits should be  
2324 calculated with reference to the worst case (the API with the smaller area under  
2325 the curve). Alternatively the content of such impurities could be calculated in  
2326 relation to their reference standards,
  - 2327 ○ when any one API is present at less than 25 mg or less than 25% of the weight  
2328 of the dosage unit, a test and limit for content uniformity is required for each  
2329 API in the FPP,
  - 2330 ○ when all APIs are present at equal or greater than 25 mg and equal or greater  
2331 than 25% of the weight of the dosage unit, a test and limit for weight variation  
2332 may be established for the FPP, in lieu of content uniformity testing;
- 2333 • modified-release products: a meaningful API release method;

- 2334 • inhalation and nasal products: consistency of delivered dose (throughout the use of the
- 2335 product), particle or droplet size distribution profiles (comparable to the product used
- 2336 in in vivo studies, where applicable) and if applicable for the dosage form, moisture
- 2337 content, leak rate, microbial limits, preservative assay, sterility and weight loss;
- 2338 • suppositories: uniformity of dosage units, melting point; and
- 2339 • transdermal dosage forms: peel or shear force, mean weight per unit area, dissolution.

2340

2341 Unless there is appropriate justification, the acceptable limit for the API content of the FPP in  
2342 the release specifications is  $\pm 5\%$  of the label claim (i.e. 95.0–105.0%).

2343

2344 Skip testing is acceptable for parameters such as identification of colouring materials and  
2345 microbial limits, when justified by the submission of acceptable supportive results for five  
2346 production batches. When skip-testing justification has been accepted, the specifications  
2347 should include a footnote, stating at minimum the following skip-testing requirements: at  
2348 minimum every tenth batch and at least one batch annually is tested. In addition, for stability-  
2349 indicating parameters such as microbial limits, testing will be performed at release and shelf-  
2350 life during stability studies.

2351

2352 Any differences between release and shelf-life tests and acceptance criteria should be clearly  
2353 indicated and justified. Note that such differences for parameters such as dissolution are  
2354 normally not accepted.

2355

2356 Reference documents: ICH Q3B, Q3C, Q6A

2357

### 2358 **3.2.P.5.2 Analytical procedures (name, dosage form)**

2359

2360 **The analytical procedures used for testing the FPP should be provided.**

2361

2362 Copies of the in-house analytical procedures used during pharmaceutical development (if used  
2363 to generate testing results provided in the PD) as well as those proposed for routine testing  
2364 should be provided. Unless modified, it is not necessary to provide copies of officially  
2365 recognized compendial analytical procedures.

2366

2367 Tables for summarizing a number of the different analytical procedures and validation  
2368 information (e.g. HPLC assay/impurity methods) can be found in the 2.3.R Regional  
2369 information section of the QOS-PD (i.e. 2.3.R.2). These tables should be used to summarize  
2370 the analytical procedures used for determination of the assay, related substances and  
2371 dissolution of the FPP.

2372

2373 Refer to section 3.2.S.4.2 of this guideline for additional guidance on analytical procedures.

2374

2375 Reference documents: ICH Q2

2376

### 2377 **3.2.P.5.3 Validation of analytical procedures (name, dosage form)**

2378

2379 **Analytical validation information, including experimental data, for the analytical**  
2380 **procedures used for testing the FPP should be provided.**

2381

2382 Copies of the validation reports for the in-house analytical procedures used during  
2383 pharmaceutical development (if used to support testing results provided in the PD) as well as  
2384 those proposed for routine testing should be provided.

2385  
2386 Tables for summarizing a number of the different analytical procedures and validation  
2387 information (e.g. HPLC assay/impurity methods, GC methods) can be found in the 2.3.R  
2388 Regional information section of the QOS-PD (i.e. 2.3.R.2). These tables should be used to  
2389 summarize the validation information of the analytical procedures used for determination of  
2390 the assay, related substances and dissolution of the FPP.

2391  
2392 As recognized by regulatory authorities and pharmacopoeias themselves, verification of  
2393 compendial methods can be necessary. The compendial methods, as published, are typically  
2394 validated based on an API or an FPP originating from a specific manufacturer. Different  
2395 sources of the same API or FPP can contain impurities and/or degradation products or  
2396 excipients that were not considered during the development of the monograph. Therefore, the  
2397 monograph and compendial method(s) should be demonstrated suitable for the control of the  
2398 proposed FPP.

2399  
2400 For officially recognized compendial FPP *assay* methods, verification should include a  
2401 demonstration of specificity, accuracy and repeatability (method precision). If an officially  
2402 recognized compendial method is used to control related substances that are not specified in  
2403 the monograph, full validation of the method is expected with respect to those related  
2404 substances.

2405  
2406 If an officially recognized compendial standard is claimed and an in-house method is used in  
2407 lieu of the compendial method (e.g. for assay or for related compounds), equivalency of the  
2408 in-house and compendial methods should be demonstrated. This could be accomplished by  
2409 performing duplicate analyses of one sample by both methods and providing the results from  
2410 the study. For related compound methods, the sample analysed should be the placebo spiked  
2411 with related compounds at concentrations equivalent to their specification limits.

2412  
2413 Reference documents: ICH Q2

2414  
2415 **3.2.P.5.4 Batch analyses (name, dosage form)**

2416  
2417 **A description of batches and results of batch analyses should be provided.**

2418  
2419 Information should include strength and batch number, batch size, date and site of production  
2420 and use (e.g. used in comparative bioavailability or biowaiver studies, preclinical and clinical  
2421 studies (if relevant), stability, pilot, scale-up and if available, production-scale batches) on  
2422 relevant FPP batches used to establish the specification(s) and evaluate consistency in  
2423 manufacturing.

2424  
2425 Analytical results tested by the company responsible for the batch release of the FPP  
2426 (generally, the applicant or the FPP manufacturer, if different from the applicant) should be  
2427 provided for not less than two batches of at least pilot scale, or in the case of an  
2428 uncomplicated<sup>2</sup> FPP (e.g. immediate-release solid FPPs (with noted exceptions), non-sterile

---

<sup>2</sup> The term "complicated FPP" includes sterile products, metered dose inhaler products, dry powder inhaler products and transdermal delivery systems. Other specific products under "complicated FPP" include ritonavir/lopinavir FDC tablets and FDCs containing rifampicin or an artemisinin. As the invitations for EOI change over time, the listing of individual "complicated" FPPs is not meaningful and applicants should contact the Head of Assessments, Prequalification of Medicines Programme, in case of doubt.

2429 solutions), not less than one batch of at least pilot scale and a second batch which may be  
2430 smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules) of each  
2431 proposed strength of the FPP. These batches should be manufactured by a procedure fully  
2432 representative of and simulating that to be applied to a full production-scale batch.  
2433

2434 The testing results should include the batch(es) used in the comparative bioavailability or  
2435 biowaiver studies. Copies of the certificates of analysis for these batches should be provided  
2436 in the PD and the company responsible for generating the testing results should be identified.  
2437

2438 The discussion of results should focus on observations noted for the various tests, rather than  
2439 reporting comments such as “all tests meet specifications”. This should include ranges of  
2440 analytical results where relevant. For quantitative tests (e.g. individual and total impurity tests  
2441 and assay tests), it should be ensured that actual *numerical results* are provided rather than  
2442 vague statements such as “within limits” or “conforms” (e.g. “levels of degradation product A  
2443 ranged from 0.2 to 0.4%”). Dissolution results should be expressed at minimum as both the  
2444 average and range of individual results. Recommendations for conducting and assessing  
2445 comparative dissolution profiles can be found in Appendix 1.  
2446

2447 A discussion and justification should be provided for any incomplete analyses (e.g. results not  
2448 tested according to the proposed specification).  
2449

2450 Reference documents: ICH Q3B, Q3C, Q6A  
2451

### 2452 **3.2.P.5.5 Characterization of impurities (name, dosage form)**

2453

2454 **Information on the characterization of impurities should be provided, if not previously**  
2455 **provided in “3.2.S.3.2 Impurities”.**  
2456

2457 A discussion should be provided of all impurities that are potential degradation products  
2458 (including those among the impurities identified in 3.2.S.3.2 as well as potential degradation  
2459 products resulting from interaction of the API with other APIs (FDCs), excipients or the  
2460 container-closure system) and FPP process-related impurities (e.g. residual solvents in the  
2461 manufacturing process for the FPP).  
2462

2463 Reference documents: ICH Q3B, Q3C, Q6A  
2464

### 2465 **3.2.P.5.6 Justification of specification(s) (name, dosage form)**

2466

2467 **Justification for the proposed FPP specification(s) should be provided.**  
2468

2469 A discussion should be provided on the omission or inclusion of certain tests, evolution of  
2470 tests, analytical procedures and acceptance criteria, differences from the officially recognized  
2471 compendial standard(s), etc. If the officially recognized compendial methods have been  
2472 modified or replaced, a discussion should be included.  
2473

2474 The justification for certain tests, analytical procedures and acceptance criteria (e.g.  
2475 degradation products, dissolution method development) may have been discussed in other  
2476 sections of the PD and does not need to be repeated here, although a cross-reference to their  
2477 location should be provided.  
2478

2479 ICH Q6A should be consulted for the development of specifications for FPPs.

2480

2481 **3.2.P.6 Reference standards or materials (name, dosage form)**

2482

2483 **Information on the reference standards or reference materials used for testing of the**  
2484 **FPP should be provided, if not previously provided in “3.2.S.5 Reference standards or**  
2485 **materials”.**

2486

2487 See section 3.2.S.5 for information that should be provided on reference standards or  
2488 materials. Information should be provided on reference materials of FPP degradation  
2489 products, where not included in 3.2.S.5.

2490

2491 Reference documents: ICH Q6A, WHO Technical Report Series, No. 943, Annex 3

2492

2493 **3.2.P.7 Container-closure system (name, dosage form)**

2494

2495 **A description of the container-closure systems should be provided, including the identity**  
2496 **of materials of construction of each primary packaging component and its specification.**  
2497 **The specifications should include description and identification (and critical dimensions,**  
2498 **with drawings where appropriate). Noncompendial methods (with validation) should be**  
2499 **included, where appropriate.**

2500

2501 **For non-functional secondary packaging components (e.g. those that neither provide**  
2502 **additional protection nor serve to deliver the product), only a brief description should be**  
2503 **provided. For functional secondary packaging components, additional information**  
2504 **should be provided.**

2505

2506 **Suitability information should be located in 3.2.P.2.**

2507

2508 The WHO *Guidelines on packaging for pharmaceutical products* (WHO Technical Report  
2509 Series, No. 902, Annex 9, 2002) and the officially recognized pharmacopoeias should be  
2510 consulted for recommendations on the packaging information for FPPs.

2511

2512 Descriptions, materials of construction and specifications (of the company responsible for  
2513 packaging the FPP, generally the FPP manufacturer) should be provided for the packaging  
2514 components that are:

- 2515 • in direct contact with the dosage form (e.g. container, closure, liner, desiccant, filler);
- 2516 • used for drug delivery (including the device(s) for multidose solutions, emulsions,  
2517 suspensions and powders/granules for such);
- 2518 • used as a protective barrier to help ensure stability or sterility; and
- 2519 • necessary to ensure FPP quality during storage and shipping.

2520

2521 Primary packaging components are those that are in direct contact with the API or FPP.

2522

2523 The specifications for the primary packaging components should include a specific test for  
2524 identification (e.g. IR). Specifications for film and foil materials should include limits for  
2525 thickness or area weight.

2526

2527 Information to establish the suitability (e.g. qualification) of the container-closure system  
2528 should be discussed in section 3.2.P.2. Comparative studies may be warranted for certain

2529 changes in packaging components (e.g. comparative delivery study (droplet size) for a change  
2530 in manufacturer of dropper tips).

2531

### 2532 **3.2.P.8 Stability (name, dosage form)**

2533

#### 2534 **3.2.P.8.1 Stability summary and conclusions (name, dosage form)**

2535

2536 **The types of studies conducted, protocols used and the results of the studies should be**  
2537 **summarized. The summary should include, for example, conclusions with respect to**  
2538 **storage conditions and shelf-life, and if applicable, in-use storage conditions and shelf-**  
2539 **life.**

2540

2541 The WHO stability guideline *Stability testing of active pharmaceutical ingredients and*  
2542 *finished pharmaceutical products* (WHO Technical Report Series, No. 953, Annex 2, 2009)  
2543 should be consulted for recommendations on the core stability data package required for the  
2544 prequalification of APIs and FPPs.

2545

2546 As outlined in the WHO stability guideline, the purpose of stability testing is to provide  
2547 evidence of how the quality of an API or FPP varies with time under the influence of a variety  
2548 of environmental factors such as temperature, humidity and light. The stability programme  
2549 also includes the study of product-related factors that influence its quality, for example,  
2550 interaction of API with excipients, container-closure systems and packaging materials.

2551

#### 2552 *Stress testing*

2553

2554 As outlined in the WHO stability guideline, photostability testing should be conducted on at  
2555 least one primary batch of the FPP if appropriate. If “protect from light” is stated in one of  
2556 the officially recognized pharmacopoeias for the API or FPP, it is sufficient to state “protect  
2557 from light” on labelling, in lieu of photostability studies, when the container-closure system is  
2558 shown to be light-protective. Additional stress testing of specific types of dosage forms may  
2559 be appropriate (e.g. cyclic studies for semisolid products, freeze-thaw studies for liquid  
2560 products).

2561

#### 2562 *Accelerated, intermediate (if necessary) and long-term testing*

2563

2564 Stability data must demonstrate stability of the medicinal product throughout its intended  
2565 shelf-life under the climatic conditions prevalent in the target countries. Merely applying the  
2566 same requirements applicable to other markets could potentially lead to substandard products,  
2567 e.g. stability studies conducted for countries in Climatic Zone I/II when the products are  
2568 supplied in Climatic Zones III and IV countries. Refer to WHO Technical Report Series, No.  
2569 953, Annex 2, Appendix 1 for information on climatic zones. Effective as of September 2011,  
2570 the required long-term storage conditions for the Prequalification Programme are  
2571 30 °C±2 °C/75%±5%RH, and after this date the long-term data submitted in the PD (see table  
2572 below) should be at these conditions. The use of alternative long-term conditions will need to  
2573 be justified and should be supported with appropriate evidence.

2574

2575 Other storage conditions are outlined in the WHO stability guideline for FPPs packaged in  
2576 impermeable and semipermeable containers and those intended for storage in a refrigerator  
2577 and in a freezer. FPPs intended for storage below –20 °C should be treated on a case-by-case  
2578 basis.

2579

2580 The minimum data required at the time of submitting the dossier (in the general case):

2581

<b>Storage temperature (°C)</b>	<b>Relative humidity (%)</b>	<b>Minimum time period (months)</b>
Accelerated 40±2	75±5	6
Intermediate *	N/A	N/A
Long-term 30±2	75±5	6

2582 \*Where long-term conditions are 30 °C±2 °C/75%±5%RH, there is no intermediate condition.

2583

2584 Refer to WHO Technical Report Series, No. 953, Annex 2 for further information regarding  
2585 the storage conditions. Reference should also be made to the Prequalification Programme  
2586 web site for any exceptions to the stated requirements.

2587

2588 To establish the shelf-life, data should be provided on not less than two batches of at least  
2589 pilot scale, or in the case of an uncomplicated FPP (e.g. immediate-release solid FPPs (with  
2590 noted exceptions), non-sterile solutions), not less than one batch of at least pilot scale and a  
2591 second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets  
2592 or capsules) of each proposed strength of the FPP. These batches should be manufactured by  
2593 a procedure fully representative of and simulating that to be applied to a full production-scale  
2594 batch.

2595

2596 The stability testing programme should be summarized and the results of stability testing  
2597 should be reported in the dossier and summarized in the tables in the QOS-PD. Bracketing  
2598 and matrixing of proportional strengths can be applied, if scientifically justified.

2599

2600 For sterile products sterility should be reported at the beginning and end of shelf-life. For  
2601 parenteral products, subvisible particulate matter should be reported frequently, but not  
2602 necessarily at every test interval. Bacterial endotoxins need only be reported at the initial test  
2603 interval. Weight loss from plastic containers should be reported over the shelf-life. In-use  
2604 periods (e.g. parenteral and ophthalmic products) should be justified with experimental data.

2605

2606 The information on the stability studies should include details such as:

- 2607 • storage conditions;
- 2608 • strength;
- 2609 • batch number, including the API batch number(s) and manufacturer(s);
- 2610 • batch size;
- 2611 • container-closure system including orientation (e.g. erect, inverted, onside) where  
2612 applicable; and
- 2613 • completed (and proposed) test intervals.

2614

2615 The discussion of results should focus on observations noted for the various tests, rather than  
2616 reporting comments such as “all tests meet specifications”. This should include ranges of  
2617 analytical results and any trends that were observed. For quantitative tests (e.g. individual and  
2618 total degradation product tests and assay tests), it should be ensured that actual numerical  
2619 results are provided rather than vague statements such as “within limits” or “conforms”.

2620 Dissolution results should be expressed at minimum as both the average and range of  
2621 individual results.

2622

2623 Applicants should consult ICH’s Q1E guideline for details on the evaluation and extrapolation  
2624 of results from stability data (e.g. if significant change was not observed within six months at  
2625 accelerated condition and the data show little or no variability, the proposed shelf-life could

2626 be up to two times the period covered by the long-term data, but should not exceed the long-  
2627 term data by 12 months).

2628

2629 *Proposed storage statement and shelf-life*

2630

2631 The proposed storage statement and shelf-life (and in-use storage conditions and in-use  
2632 period, if applicable) for the FPP should be provided.

2633

2634 The recommended labelling statements for use, based on the stability studies, are provided in  
2635 the WHO stability guideline.

2636

2637 Reference documents: WHO Technical Report Series, No. 953, Annex 2, ICH Q1A, Q1B,  
2638 Q1C, Q1D, Q1E, Q3B, Q6A

2639

2640 **3.2.P.8.2 Post-approval stability protocol and stability commitment (name, dosage form)**

2641

2642 **The post-approval stability protocol and stability commitment should be provided.**

2643

2644 *Primary stability study commitment*

2645

2646 When available long-term stability data on primary batches do not cover the proposed shelf-  
2647 life granted at the time of assessment of the PD, a commitment should be made to continue  
2648 the stability studies in order to firmly establish the shelf-life. A written commitment (signed  
2649 and dated) to continue long-term testing over the shelf-life period should be included in the  
2650 dossier.

2651

2652 *Commitment stability studies*

2653

2654 The long-term stability studies for the *Commitment batches* should be conducted through the  
2655 proposed shelf-life on at least three production batches of each strength in each container-  
2656 closure system. Where stability data was not provided for three production batches of each  
2657 strength, a written commitment (signed and dated) should be included in the dossier.

2658

2659 *Ongoing stability studies*

2660

2661 As described in the WHO stability guideline, an *ongoing stability programme* is established to  
2662 monitor the product over its shelf-life and to determine that the product remains and can be  
2663 expected to remain within specifications under the storage conditions on the label. Unless  
2664 otherwise justified, at least one batch per year of product manufactured in every strength and  
2665 every container-closure system, if relevant, should be included in the stability programme  
2666 (unless none is produced during that year). Bracketing and matrixing may be applicable. A  
2667 written commitment (signed and dated) to this effect should be included in the dossier.

2668

2669 Any differences in the stability protocols used for the primary batches and those proposed for  
2670 the *commitment batches* or *ongoing batches* should be scientifically justified.

2671

2672 Reference documents: ICH Q1A

2673

2674 **3.2.P.8.3 Stability data (name, dosage form)**  
2675

2676 **Results of the stability studies should be presented in an appropriate format (e.g.**  
2677 **tabular, graphical, narrative). Information on the analytical procedures used to**  
2678 **generate the data and validation of these procedures should be included.**  
2679

2680 **Information on characterization of impurities is located in 3.2.P.5.5.**  
2681

2682 The actual stability results/reports used to support the proposed shelf-life should be provided  
2683 in the PD. For quantitative tests (e.g. individual and total degradation product tests and assay  
2684 tests), it should be ensured that actual numerical results are provided rather than vague  
2685 statements such as “within limits” or “conforms”. Dissolution results should be expressed at  
2686 minimum as both the average and range of individual results.  
2687

2688 Reference documents: ICH Q1A, Q1B, Q1C, Q1D, Q1E, Q2  
2689

2690 **3.2.A Appendices**  
2691

2692 **3.2.A.1 Facilities and equipment**  
2693

2694 Not applicable (i.e. not a biotech product).  
2695

2696 **3.2.A.2 Adventitious agents safety evaluation**  
2697

2698 **3.2.A.3 Novel excipients**  
2699

2700 Novel excipients are not accepted in the Prequalification Programme.  
2701

2702 **3.2.R Regional information**  
2703

2704 **3.2.R.1 Production documentation**  
2705

2706 **3.2.R.1.1 Executed production documents**  
2707

2708 A minimum of two batches of at least pilot scale, or in the case of an uncomplicated FPP (e.g.  
2709 immediate-release solid FPPs (with noted exceptions), non-sterile solutions), not less than one  
2710 batch of at least pilot scale (the batch used in comparative bioavailability or biowaiver  
2711 studies) and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or  
2712 50 000 tablets or capsules), should be manufactured for each strength. These batches should  
2713 be manufactured by a procedure fully representative of and simulating that to be applied to a  
2714 full production-scale batch.  
2715

2716 For solid oral dosage forms, *pilot scale* is generally, at a minimum, one-tenth that of full  
2717 production scale or 100 000 tablets or capsules, whichever is the larger.  
2718

2719 Copies of the executed production documents should be provided for the batches used in the  
2720 comparative bioavailability or biowaiver studies. Any notations made by operators on the  
2721 executed production documents should be clearly legible.  
2722

2723 If not included in the executed batch records through sufficient in-process testing, data should  
2724 be provided for the batch used in comparative bioavailability or biowaiver studies that

2725 demonstrates the uniformity of this batch. The data to establish the uniformity of the biobatch  
2726 should involve testing to an extent greater than that required in routine quality control.

2727

2728 English translations of executed records should be provided, where relevant.

2729

### 2730 **3.2.R.1.2 Master production documents**

2731

2732 Copies of the FPP master production documents should be provided for each proposed  
2733 strength, commercial batch size and manufacturing site.

2734

2735 The details in the master production documents should include, but not be limited to, the  
2736 following:

2737

a) master formula;

2738

b) dispensing, processing and packaging sections with relevant material and operational  
2739 details;

2740

c) relevant calculations (e.g. if the amount of API is adjusted based on the assay results  
2741 or on the anhydrous basis);

2742

d) identification of all equipment by, at minimum, type and working capacity (including  
2743 make, model and equipment number, where possible);

2744

e) process parameters (e.g. mixing time, mixing speed, milling screen size, processing  
2745 temperature range, granulation end-point, tablet machine speed (expressed as target  
2746 and range));

2747

f) list of in-process tests (e.g. appearance, pH, assay, blend uniformity, viscosity, particle  
2748 size distribution, LOD, weight variation, hardness, disintegration time, weight gain  
2749 during coating, leaker test, minimum fill, clarity, filter integrity checks) and  
2750 specifications;

2751

g) sampling plan with regard to the:

2752

i. steps where sampling should be done (e.g. drying, lubrication, compression),

2753

ii. number of samples that should be tested (e.g. for blend uniformity testing of  
2754 low dose FPPs, blend drawn using a sampling thief from x positions in the  
2755 blender),

2756

iii. frequency of testing (e.g. weight variation every x minutes during compression  
2757 or capsule filling);

2758

h) precautions necessary to ensure product quality (e.g. temperature and humidity  
2759 control, maximum holding times);

2760

i) for sterile products, reference to SOPs in appropriate sections and a list of all relevant  
2761 SOPs at the end of the document;

2762

j) theoretical and actual yield; and

2763

k) compliance with the GMP requirements.

2764

2765

Reference documents: WHO Technical Report Series, Nos 902 and No. 908

2766

2767 **3.2.R.2 Analytical procedures and validation information**  
2768

2769 The tables presented in section 2.3.R.2 in the QOS-PD template should be used to summarize  
2770 the analytical procedures and validation information from sections 3.2.S.4.2, 3.2.S.4.3,  
2771 2.3.S.4.4 (c), 2.3.S.7.3 (b), 3.2.P.5.2 and 3.2.P.5.3, where relevant.  
2772

2773 4.3 Literature references  
2774

2775 References to the scientific literature relating to both the API and FPP should be included in  
2776 this section of the PD when appropriate.  
2777

2778 **5. REFERENCES**

- 2779 1. Guidelines on packaging for pharmaceutical products. In: *WHO Expert Committee on*  
2780 *Specifications for Pharmaceutical Preparations. Thirty-sixth report.* Geneva, World  
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2785 Geneva, World Health Organization, 2011, Annex 6 (WHO Technical Report Series,  
2786 No. 961).  
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2792
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2794 via medicinal products. In: *WHO Expert Committee on Specifications for*  
2795 *Pharmaceutical Preparations. Thirty-seventh report.* Geneva, World Health  
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2797
- 2798 5. Guidelines for registration of fixed-dose combination medicinal products. Appendix  
2799 3: Pharmaceutical development (or preformulation) studies. Table A1: Typical stress  
2800 conditions in preformulation stability studies. In: *WHO Expert Committee on*  
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2808
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- 2814 8. Guidelines on active pharmaceutical ingredient master file procedure. In: *WHO Expert*  
2815 *Committee on Specifications for Pharmaceutical Preparations. Forty-second report.*

- 2816 Geneva, World Health Organization, 2008, Annex 4 (WHO Technical Report Series,  
2817 No. 948).  
2818
- 2819 9. Stability testing of active pharmaceutical ingredients and finished pharmaceutical  
2820 products. In: *WHO Expert Committee on Specifications for Pharmaceutical*  
2821 *Preparations. Forty-third report*. Geneva, World Health Organization, 2009, Annex 2  
2822 (WHO Technical Report Series, No. 953).  
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2825 *Committee on Specifications for Pharmaceutical Preparations. Forty-third report*.  
2826 Geneva, World Health Organization, 2011, Annex 10 (WHO Technical Report Series,  
2827 No. 961).  
2828
- 2829 11. WHO good distribution practices for pharmaceutical products. In: *WHO Expert*  
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2831 Geneva, World Health Organization, 2010, Annex 5 (WHO Technical Report Series,  
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2833

Revised draft for comment

2834 **APPENDIX 1**  
2835 **RECOMMENDATIONS FOR CONDUCTING AND ASSESSING COMPARATIVE**  
2836 **DISSOLUTION PROFILES**  
2837  
2838

2839 The dissolution measurements of the two FPPs (e.g. test and reference (comparator), or two  
2840 different strengths) should be made under the same test conditions. A minimum of three time  
2841 points (zero excluded) should be included, the time points for both reference (comparator) and  
2842 test product being the same. The sampling intervals should be short for a scientifically sound  
2843 comparison of the profiles (e.g. 5, 10, 15, 20, 30, 45 (60, 90, 120) minutes). Inclusion of the  
2844 15 minute time point in the schedule is of strategic importance for profile similarity  
2845 determinations (very rapidly dissolving scenario). For extended-release FPPs, the time points  
2846 should be set to cover the entire time period of expected release, e.g. 1, 2, 3, 5 and 8 hours for  
2847 a 12-hour release and additional test intervals for longer duration of release.  
2848

2849 Studies should be performed in at least three (3) media covering the physiological range,  
2850 including pH 1.2 hydrochloric acid, pH 4.5 buffer and pH 6.8 buffer. *International*  
2851 *Pharmacopoeia* buffers are recommended; alternative compendia buffers with the same pH  
2852 and buffer capacity are also accepted. Water may be considered as an additional medium,  
2853 especially when the API is unstable in the buffered media to the extent that the data is  
2854 unusable.  
2855

2856 If both the test and reference (comparator) products show more than 85% dissolution in 15  
2857 minutes, the profiles are considered similar (no calculations required). Otherwise:  
2858

- 2859 • *similarity* of the resulting comparative dissolution profiles should be calculated using  
2860 the following equation that defines a similarity factor ( $f_2$ ):  
2861

$$2862 \quad f_2 = 50 \text{ LOG } \{ [1 + 1/n \sum_{i=1}^n (R_i - T_i)^2]^{-0.5} \times 100 \}$$

2863

2864 where  $R_i$  and  $T_i$  are the mean percent API dissolved in reference (comparator) and test  
2865 product, respectively, at each time point. An  $f_2$  value between 50 and 100 suggests the  
2866 two dissolution profiles are similar;  
2867

- 2868 • a maximum of one time-point should be considered after 85% dissolution of the  
2869 reference (comparator) product has been reached. In the case where 85% dissolution  
2870 cannot be reached due to poor solubility of the API, the dissolution should be  
2871 conducted until an asymptote (plateau) has been reached;  
2872
- 2873 • at least 12 units should be used for each profile determination. Mean dissolution  
2874 values can be used to estimate the similarity factor,  $f_2$ . To use mean data, the %  
2875 coefficient of variation at the first time point should be not more than 20% and at other  
2876 time points should be not more than 10%;  
2877
- 2878 • when delayed-release products (e.g. enteric coated) are being compared, the  
2879 recommended conditions are acid medium (pH 1.2) for 2 hours and buffer pH 6.8  
2880 medium;  
2881

- 2882
- 2883
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- 2888
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- when comparing extended-release beaded capsules, where different strengths have been achieved solely by means of adjusting the number of beads containing the API, one condition (normally the release condition) will suffice; and
  - surfactants should be avoided in comparative dissolution testing. A statement that the API is not soluble in any of the media is not sufficient and profiles in absence of surfactance should be provided. The rationale for the choice and concentration of surfactant should be provided. The concentration of the surfactant should be such that the discriminatory power of the test will not be compromised.

Revised draft for comment

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**APPENDIX 2**  
**PRODUCT QUALITY REVIEW REQUIREMENTS FOR *ESTABLISHED***  
***MULTISOURCE PRODUCTS***

For an established multisource product a product quality review may satisfy the requirements of sections 3.2.P.2.2.1 (a), 3.2.P.2.3 (a) and 3.2.P.3.5 of the PD and QOS-PD.

A product quality review should be submitted with the objective of verifying the consistency of the quality of the FPP and its manufacturing process.

Rejected batches should not be included in the analysis but must be reported separately together with the reports of failure investigations, as indicated below.

Reviews should be conducted with not less than 10 consecutive batches manufactured over the period of the last 12 months, or, where 10 batches were not manufactured in the last 12 months, not less than 25 consecutive batches manufactured over the period of the last 36 months and should include at least:

1. A review of starting and primary packaging materials used in the FPP, especially those from new sources.
2. A tabulated review and statistical analysis of quality control and in-process control results.
3. A review of all batches that failed to meet established specification(s).
4. A review of all critical deviations or non-conformances and related investigations.
5. A review of all changes carried out to the processes or analytical methods.
6. A review of the results of the stability-monitoring programme.
7. A review of all quality-related returns, complaints and recalls, including export-only medicinal products.
8. A review of the adequacy of previous corrective actions.
9. A list of validated analytical and manufacturing procedures and their revalidation dates.

Notes

Reviews must include data from all batches manufactured during the review period.

Data should be presented in tabular or graphical form (i.e. charts or graphs), when applicable.

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