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

***DRAFT FOR COMMENT***

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Any further action as required	...

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Draft for comment

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85 **1. INTRODUCTION**

86

87 1.1 Background

88

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

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

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

100

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

107

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

112

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

118

119 1.2 Objectives

120

121 This guideline is intended to:

122

- 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
- 126 • fully adopt the modular format of the *Common Technical Document - Quality (M4Q)*  
127 as developed by ICH; and
- 128
- 129 • provide guidance on the technical and other general data requirements.

130

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

133

134 1.3 Scope

135

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

141

142 1.4 General principles

143

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

147

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

151

- 152 • “Drug substance” is replaced with “active pharmaceutical ingredient (or API)”;
- 153 • “Drug product” is replaced with “finished pharmaceutical product (or FPP)”;
- 154 • “application” is replaced with “product dossier (or PD)”;
- 155 • “combination product” is replaced with “fixed-dose combination (or FDC)”;
- 156 • “clinical batches” is replaced with “comparative bioavailability or biowaiver batches”.

157

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

162

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

169

170 Scientific literature may be appropriate to fulfil the requirements for some of the information  
171 or parameters outlined in this guideline (e.g. qualification of specified identified impurities).  
172 Furthermore, the requirements outlined in certain sections may not be applicable for the  
173 proposed API or FPP. In these situations, a summary and the full reference to the scientific  
174 literature should be provided or the non-applicability of the requested information should be  
175 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 SwissMedic, Health  
Canada and World Health Organization (WHO) (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).*

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## 1.5 Guidance on format

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

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

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

- the *Open part* (non-proprietary information) of each APIMF should always be included *in its entirety* in the PD, as an annex to 3.2.S.
- for an FPP containing more than one API: one complete “3.2.S” section should be provided for one API, *followed by* other complete “3.2.S” sections for each other API.
- for an API from multiple manufacturers: one complete “3.2.S” section should be provided for the API from one manufacturer, *followed by* other complete “3.2.S” sections for each other API manufacturer.
- for an FPP with multiple strengths (e.g. 10, 50, 100 mg): one complete “3.2.P” section should be provided with the information for the different strengths provided *within* the subsections. One complete copy of the PD should be provided for each FPP strength.
- for an FPP with multiple container closure systems (e.g. bottles and unit dose blisters): one complete “3.2.P” section should be provided with the information for the different presentations provided *within* the subsections.
- for multiple FPPs (e.g. tablets and a parenteral product): a separate dossier is required for each FPP.
- for an FPP supplied with reconstitution diluent(s), one complete “3.2.P” section should be provided for the FPP, *followed by* the information on the diluent(s) in a separate part “3.2.P”, as appropriate.

217 **2. GLOSSARY**

218

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

223

224 *active pharmaceutical ingredient (API)*

225 Any substance or combination of substances used in a finished pharmaceutical product (FPP),  
226 intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis,  
227 cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring,  
228 correcting or modifying physiological functions in human beings (ref. WHO Technical Report  
229 Series, No. 953, Annex 3, 2009).

230

231 *API starting material*

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

237

238 *applicant*

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

243

244 *BCS highly soluble*

245 An API for which the highest dose recommended by WHO (if the API appears on the *WHO*  
246 *Model List of Essential Medicines*) or highest dose strength available on the market as an oral  
247 solid dosage form (if the API does not appear on the *WHO Model List of Essential*  
248 *Medicines*) is soluble in 250 ml or less of aqueous media over the pH range of 1.2–6.8 at  
249 37°C (ref. WHO Technical Report Series, No. 937, Annex 7, 2006).

250

251 *commitment batches*

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

255

256 *comparator product*

257 A pharmaceutical product with which the generic product is intended to be interchangeable in  
258 clinical practice. The comparator product will normally be the innovator product for which  
259 efficacy, safety and quality have been established (ref. WHO Technical Report Series, No.  
260 937, Annex 7, 2006). For the Prequalification Programme, the selection of the comparator  
261 product is based on the information presented under Guidance on Bioequivalence Studies  
262 available on the Prequalification website.

263

264 *established multisource (generic) product*

265 A multisource product that has been marketed by the applicant or manufacturer associated  
266 with the dossier for at least five years and for which at least 10 production batches were

267 produced over the previous year, or, if less than 10 batches were produced in the previous  
268 year, not less than 25 batches were produced in the previous three years.

269

270 *existing API*

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

275

276 *finished pharmaceutical product (FPP)*

277 A finished dosage form of a pharmaceutical product, which has undergone all stages of  
278 manufacture, including packaging in its final container and labelling (ref. WHO Technical  
279 Report Series, No. 953, Annex 3, 2009).

280

281 *innovator pharmaceutical product*

282 Generally the pharmaceutical product that was first authorized for marketing (normally as a  
283 patented product) on the basis of documentation of efficacy, safety and quality (ref. WHO  
284 Technical Report Series, No. 937, Annex 7, 2006).

285

286 *manufacturer*

287 A company that produces, packages, repackages, labels and/or relabels pharmaceutical  
288 products (ref. WHO Technical Report Series, No. 953, Annex 3, 2009).

289

290 *multisource (generic) pharmaceutical products*

291 Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be  
292 therapeutically equivalent. Multisource pharmaceutical products that are therapeutically  
293 equivalent are interchangeable (ref. WHO Technical Report Series, No. 937, Annex 7, 2006).

294

295 *officially recognized pharmacopoeia (or compendia)*

296 Those pharmacopoeias recognized in the WHO Prequalification Programme (i.e. The  
297 International Pharmacopoeia (Ph.Int.), the European Pharmacopoeia (Ph.Eur.), the British  
298 Pharmacopoeia (BP), the Japanese Pharmacopoeia (JP) and the United States Pharmacopoeia  
299 (USP)).

300

301 *ongoing stability study*

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

306

307 *pilot- scale batch*

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

313

314 *primary batch*

315 A batch of an API or FPP used in a stability study, from which stability data are submitted in  
316 a registration application for the purpose of establishing a re-test period or shelf-life (ref.  
317 WHO Technical Report Series, No. 953, Annex 2, 2009). For the Prequalification

318 Programme, primary batch requirements are outlined in 3.2.S.7.1 and 3.2.P.8.1 for the API  
319 and FPP, respectively.

320

321 *production batch*

322 A batch of an API or FPP manufactured at production scale by using production equipment in  
323 a production facility as specified in the application (ref. WHO Technical Report Series, No.  
324 953, Annex 2, 2009).

325

326 *starting materials for synthesis*

327 Materials that mark the beginning of the manufacturing process as described in an application  
328 or in an APIMF. A starting material for a synthetic API is a chemical compound of defined  
329 molecular structure that contributes to the structure of the API. See also *API starting material*.

330

### 331 3. QUALITY SUMMARIES

332

333 3.1 Module 2.3: Quality overall summary – product dossiers (QOS-PD)

334

335 **The Quality Overall Summary (QOS) is a summary that follows the scope and the**  
336 **outline of the Body of Data in Module 3. The QOS should not include information, data**  
337 **or justification that was not already included in Module 3 or in other parts of the CTD.**

338

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

346

347 The WHO *Quality overall summary – product dossiers (QOS-PD)* template should be  
348 completed for multisource pharmaceutical products containing APIs of synthetic or semi-  
349 synthetic origin (see 1.3 Scope for further clarification) and their corresponding FPPs.

350

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

354

355 The use of tables to summarize the information is encouraged, where possible. The tables  
356 included in the template may need to be expanded, as necessary. These tables are included as  
357 illustrative examples of how to summarize information. Other approaches to summarize the  
358 information can be used if they fulfil the same purpose.

359

360 3.2 Module 1.4.2: Quality information summary (QIS)

361

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

368

369 The QIS template is structured according to the numbering and section headings of the ICH  
370 M4Q (CTD-Q) guideline to permit the rapid assembly of the QIS by copying requisite  
371 information from the corresponding portions of the QOS-PD filed with the PD. It is  
372 acknowledged that the numbering of the sections in the QIS may not be entirely sequential.  
373 Those sections not considered necessary to be included in the QIS have been removed (e.g.  
374 2.3.S.5 Reference standards or materials) and the remaining sections have retained their  
375 numbering to be consistent with the original PD.

376  
377 The QIS will serve as an official reference document in the course of GMP inspections,  
378 variation assessments and requalification assessments as performed by WHO.

#### 379 380 **4. MODULE 3: QUALITY**

##### 381 382 4.1 Table of contents of Module 3

383

384 **A Table of Contents for the filed product dossier should be provided.**

385

##### 386 4.2 Body of data

387

#### 388 **3.2.S Drug substance (or active pharmaceutical ingredient (API))**

389

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

391

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

395

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

400

- 401 • *Option 1: Certificates of Suitability of the European Pharmacopoeia (CEP)*

402

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

407

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

413

414 Along with the CEP, the applicant should supply the following information in the  
415 dossier, with data summarized in the QOS-PD.

416

- 417 ○ *3.2.S.1.3 General properties* - discussions on any additional applicable  
418 physicochemical and other relevant API properties that are not controlled by

- 419 the CEP and Ph.Eur. monograph, e.g. solubilities and polymorphs as per  
420 guidance in this section.
- 421 ○ 3.2.S.3.1 *Elucidation of structure and other characteristics* - studies to identify
  - 422 polymorphs (exception: where the CEP specifies a polymorphic form) and
  - 423 particle size distribution, where applicable, as per guidance in this section.
  - 424 ○ 3.2.S.4.1 *Specification* - the specifications of the FPP manufacturer including
  - 425 all tests and limits of the CEP and Ph.Eur. monograph and any additional tests
  - 426 and acceptance criteria that are not controlled in the CEP and Ph.Eur.
  - 427 monograph, such as polymorphs and/or particle size distribution.
  - 428 ○ 3.2.S.4.2 / 3.2.S.4.3 *Analytical procedures and validation* – for any tests in
  - 429 addition to those in the CEP and Ph.Eur. monograph.
  - 430 ○ 3.2.S.4.4 *Batch analysis* - results from three batches of at least pilot scale,
  - 431 demonstrating compliance with the FPP manufacturer’s API specifications.
  - 432 ○ 3.2.S.6 *Container closure system* - specifications including descriptions and
  - 433 identification of primary packaging components. Exception: where the CEP
  - 434 specifies a re-test period.
  - 435 ○ 3.2.S.7 *Stability* - exception: where the CEP specifies a re-test period that is the
  - 436 same as or of longer duration than the re-test period proposed by the applicant.
  - 437

438 In the case of sterile APIs, it should be noted that sterilization of the API is generally  
439 regarded by the WHO Prequalification Programme and the licensing authorities as part  
440 of finished product manufacture. Therefore data on the sterilization process of the  
441 API, including validation data, should be included in the PD.

442

- 443 • *Option 2: Active pharmaceutical ingredient master file (APIMF) procedure*
- 444

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

449

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

454

- 455 *General information* S.1.1 through S.1.3

- 456 *Manufacture* S.2

- 457 *Manufacturer(s)* S.2.1

- 458 *Description of manufacturing process and process controls* S.2.2

- 459 *Controls of critical steps and intermediates* S.2.4

- 460 *Elucidation of structure and other characteristics* S.3.1

- 461 *Impurities* S.3.2

- 462 *Control of the API* S.4.1 through S.4.5

- 463 *Reference standards or materials* S.5

- 464 *Container closure system* S.6

- 465 *Stability* S.7.1 through S.7.3

466

467 It is the responsibility of the applicant to ensure that the complete APIMF (i.e. both the  
468 applicant’s *Open part* and the API manufacturer’s *Restricted part*) is supplied to WHO

469 directly by the API manufacturer and that the applicant has access to the relevant  
470 information in the APIMF concerning the current manufacture of the API.

471  
472 A copy of the letter of access should be provided in the PD *Module 1*.

473  
474 APIMF holders can use the guidance provided for the option “Full details in the PD”  
475 for preparation of the relevant sections of the Open and Restricted parts of their  
476 APIMFs.

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

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

485  
486 **3.2.S.1 General information (name, manufacturer)**

487  
488 **3.2.S.1.1 Nomenclature (name, manufacturer)**

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

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

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

504  
505 Where an API is formed in situ during FPP manufacture (e.g. by chemical reaction), both the  
506 starting material(s) and the in situ formed API should be described (see for instance  
507 Ciprofloxacin Intravenous Infusion BP). Starting materials for in situ API preparation should  
508 be treated as APIs in the Section 3.2.S of the PD. For instance, in the case of Ciprofloxacin  
509 Intravenous Infusion BP, ciprofloxacin and lactic acid would be treated as APIs in the  
510 PD when they are used for the in situ preparation of ciprofloxacin lactate.

511  
512 **3.2.S.1.2 Structure (name, manufacturer)**

513  
514 **The structural formula, including relative and absolute stereochemistry, the molecular**  
515 **formula, and the relative molecular mass should be provided.**

516  
517 This information should be consistent with that provided in Section 3.2.S.1.1. For APIs  
518 existing as salts, the molecular mass of the free base or acid should also be provided.

519

520 **3.2.S.1.3 General properties (name, manufacturer)**

521

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

523

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

526

527 The physical and chemical properties of the API should be discussed including the physical  
528 description, solubilities in common solvents (e.g. water, alcohols, dichloromethane, acetone),  
529 quantitative aqueous pH solubility profile (e.g. pH 1 to 6.8, dose/solubility volume),  
530 polymorphism, pH and pKa values, UV absorption maxima and molar absorptivity, melting  
531 point, refractive index (for a liquid), hygroscopicity, partition coefficient, etc (see table in the  
532 QOS-PD). This list is not intended to be exhaustive, but provides an indication as to the type  
533 of information that could be included.

534

535 Some of the more relevant properties to be considered for APIs are discussed below in greater  
536 detail.

537

538 *Physical description*

539

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

543

544 *Solubilities/quantitative aqueous pH solubility profile*

545

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

547

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

550

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

554

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

556

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

557

558 \* corresponding to the lowest solubility determined over the physiological pH range (pH 1.2  
559 to 6.8) and temperature ( $37 \pm 0.5^\circ\text{C}$ ).

560

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

563

564 For example, compound A has as its lowest solubility at  $37 \pm 0.5^\circ\text{C}$ , 1.0 mg/ml at pH 6.8 and  
565 is available in 100 mg, 200 mg and 400 mg strengths. This API would not be considered a  
566 BCS *highly soluble* API as its dose/solubility volume is greater than 250 ml (400 mg/1.0  
567 mg/ml = 400 ml).

568

569 *Polymorphism*

570

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

573

- 574 • the polymorphic form(s) present in the proposed API should be listed in Section  
575 3.2.S.1.3;
- 576
- 577 • the description of manufacturing process and process controls (3.2.S.2.2) should  
578 indicate which polymorphic form is manufactured, where relevant;
- 579
- 580 • the literature references or studies performed to identify the potential polymorphic  
581 forms of the API, including the study results, should be provided in Section 3.2.S.3.1;
- 582
- 583 • if a polymorphic form is to be defined or limited (e.g. for APIs that are not *BCS highly*  
584 *soluble* and/or where polymorphism has been identified as an issue), details should be  
585 included in 3.2.S.4.1 through 3.2.S.4.5.
- 586

587

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

588

589 *Particle size distribution*

590

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

594

595 *Information from literature*

596

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

599

600 Reference documents: ICH Q6A

601

602 **3.2.S.2           Manufacture (name, manufacturer)**

603

604 **3.2.S.2.1       Manufacturer(s) (name, manufacturer)**

605

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

609

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

613

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

617

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

620

621 **3.2.S.2.2 Description of manufacturing process and process controls**  
622 **(name, manufacturer)**

623

624 **The description of the API manufacturing process represents the applicant's**  
625 **commitment for the manufacture of the API. Information should be provided to**  
626 **adequately describe the manufacturing process and process controls. For example:**

627

628 **A flow diagram of the synthetic process(es) should be provided that includes molecular**  
629 **formulae, weights, yield ranges, chemical structures of starting materials, intermediates,**  
630 **reagents and API reflecting stereochemistry, and identifies operating conditions and**  
631 **solvents.**

632

633 **A sequential procedural narrative of the manufacturing process should be submitted.**  
634 **The narrative should include, for example, quantities of raw materials, solvents,**  
635 **catalysts and reagents reflecting the representative batch scale for commercial**  
636 **manufacture, identification of critical steps, process controls, equipment and operating**  
637 **conditions (e.g. temperature, pressure, pH, time).**

638

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

642

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

651

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

654

655 As discussed in ICH Q7 and WHO Technical Report Series, No. 957 Annex 2, the point at  
656 which the *API starting material* is introduced into the manufacturing process is the starting  
657 point of the application of GMP requirements. The *API starting material* itself needs to be  
658 proposed and justified by the manufacturer and accepted as such by assessors. This  
659 justification should be documented and be available for review by WHO GMP inspectors.

660

661 The *API starting material* should be fully characterized with respect to identity and purity. In  
662 addition, the steps prior to the step where the *API starting material* appears, which may  
663 involve *starting materials for synthesis*, should be available at least in the form of a flow  
664 chart. The *starting material for synthesis* defines the starting point in the manufacturing  
665 process for an API to be described in an application.

666

667 The applicant should propose and justify which substances should be considered as *starting*  
668 *materials for synthesis*. See section 3.2.S.2.3 for further guidance.

669

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

678

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

682

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

686

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

689

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

692

693 Justification should be provided for alternate manufacturing processes. Alternate processes  
694 should be explained with the same level of detail as the primary process. It should be  
695 demonstrated that batches obtained by the alternate processes have the same impurity profile  
696 as the principal process. If the obtained impurity profile is different it should be demonstrated  
697 to be acceptable according to the requirements described under S.3.2.

698

699 It is acceptable to provide information on pilot scale manufacture, provided it is representative  
700 of production scale and scale-up is reported immediately to WHO according to the  
701 requirements of the WHO variation guideline (ref: WHO Technical Report Series, No. 943,  
702 Annex 6).

703

### 704 **3.2.S.2.3 Control of materials (name, manufacturer)**

705

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

711

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

714

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

717

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

719

- 720 • be a synthetic precursor of one or more synthesis steps prior to the final API  
721 intermediate. Acids, bases, salts, esters and similar derivatives of the API, as well as  
722 the racemate of a single enantiomer API, are not considered final intermediates;
- 723 • be a well characterized, isolated and purified substance with its structure fully  
724 elucidated including its stereochemistry (when applicable);
- 725 • have well defined specifications that include among others one or more specific  
726 identity tests and tests and limits for assay and specified, unspecified and total  
727 impurities; and
- 728 • be incorporated as a significant structural fragment into the structure of the API.  
729

730 For each starting material, the name and manufacturing site address of the manufacturer  
731 should be indicated. If there are several manufacturers, it should be clarified whether the  
732 starting material obtained from different sources is prepared by the same route of synthesis or  
733 if different routes are used. Specifications proposed for the starting material should apply to  
734 the material from each source.  
735

736 Copies of the specifications for the materials used in the synthesis, extraction, isolation and  
737 purification steps should be provided in the PD, including starting materials, reagents,  
738 solvents, catalysts and recovered materials. Confirmation should be provided that the  
739 specifications apply to materials used at each manufacturing site. A certificate of analysis of  
740 the starting material for synthesis should be provided. A summary of the information on  
741 starting materials should be provided in the QOS-PD.  
742

743 The carry-over of impurities of the starting materials for synthesis into the final API should be  
744 considered and discussed.  
745

746 A letter of attestation should be provided confirming that the API and the starting materials  
747 and reagents used to manufacture the API are *without* risk of transmitting agents of animal  
748 spongiform encephalopathies.  
749

750 When available, a CEP demonstrating TSE-compliance should be provided. A complete copy  
751 of the CEP (including any annexes) should be provided in Module 1.  
752

753 Reference documents: ICH Q6A  
754

#### 755 **3.2.S.2.4 Controls of critical steps and intermediates (name, manufacturer)**

756

757 **Critical steps: Tests and acceptance criteria (with justification including experimental**  
758 **data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing process to**  
759 **ensure that the process is controlled should be provided.**  
760

761 **Intermediates: Information on the quality and control of intermediates isolated during**  
762 **the process should be provided.**  
763

764 Where the APIMF procedure is used a cross-reference to the Restricted part of the APIMF is  
765 considered sufficient for this section of the PD, with the exception of information that is also  
766 relevant for the applicant (ref. APIMF guideline in WHO Technical Report Series, No. 948,  
767 Annex 4).  
768

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

771  
772 The critical steps should be identified. These can be among others: steps where significant  
773 impurities are removed or introduced, steps introducing an essential molecular structural  
774 element such as a chiral centre or resulting in a major chemical transformation, steps having  
775 an impact on solid-state properties and homogeneity of the API that may be relevant for use in  
776 solid dosage forms.

777  
778 Specifications for isolated intermediates should be provided and should include tests and  
779 acceptance criteria for identity, purity and assay, where applicable.

780  
781 Reference documents: ICH Q6A

782  
783 **3.2.S.2.5      *Process validation and/or evaluation (name, manufacturer)***

784  
785 **Process validation and/or evaluation studies for aseptic processing and sterilisation**  
786 **should be included.**

787  
788 Where the APIMF procedure is used, a cross-reference to the Restricted part of the APIMF is  
789 considered sufficient for this section of the PD.

790  
791 The following requirements apply to the third option for submission of API information,  
792 where full details are provided in the dossier.

793  
794 It is expected that the manufacturing processes for all APIs are properly controlled. If the API  
795 is prepared as sterile, a complete description should be provided for aseptic processing and/or  
796 sterilization methods. The controls used to maintain the sterility of the API during storage and  
797 transportation should also be provided. Alternate processes should be justified and described  
798 (see guidance in 3.2.S.2.2 for the level of detail expected).

799  
800 **3.2.S.2.6      *Manufacturing process development (name, manufacturer)***

801  
802 **A description and discussion should be provided of the significant changes made to the**  
803 **manufacturing process and/or manufacturing site of the API used in producing**  
804 **comparative bioavailability or biowaiver, scale-up, pilot, and, if available, production**  
805 **scale batches.**

806  
807 **Reference should be made to the API data provided in section 3.2.S.4.4.**

808  
809 Where the APIMF procedure is used, a cross-reference to the Restricted part of the APIMF is  
810 considered sufficient for this section of the PD.

811  
812 **3.2.S.3          *Characterization (name, manufacturer)***

813  
814 **3.2.S.3.1      *Elucidation of structure and other characteristics (name, manufacturer)***

815  
816 **Confirmation of structure based on, e.g. synthetic route and spectral analyses should be**  
817 **provided. Information such as the potential for isomerism, the identification of**  
818 **stereochemistry, or the potential for forming polymorphs should also be included.**

819

820 *Elucidation of structure*

821

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

827

828 For APIs that are not described in an officially recognized pharmacopoeia, the studies carried  
829 out to elucidate and/or confirm the chemical structure normally include elemental analysis,  
830 infrared (IR), ultraviolet (UV), nuclear magnetic resonance (NMR) and mass spectra (MS)  
831 studies. Other tests could include X-ray powder diffraction (XRPD) and differential scanning  
832 calorimetry (DSC).

833

834 For APIs that are described in an officially recognized pharmacopoeia, it is generally  
835 sufficient to provide copies of the IR spectrum of the API from each of the proposed  
836 manufacturer(s) run concomitantly with a pharmacopoeial reference standard. See Section  
837 3.2.S.5 for details on acceptable reference standards or materials.

838

839 *Isomerism/Stereochemistry*

840

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

844

845 For non-pharmacopoeial APIs, unequivocal proof of configuration of asymmetric centers such  
846 as X-ray of a single crystal should be provided when a single enantiomer of the API is  
847 claimed.

848

849 A discussion should be included of the possible isomers that can result from the  
850 manufacturing process, the steps where they were introduced or formed and a summary of the  
851 results of the studies carried out to investigate the physical, chemical and biological properties  
852 of these isomers. If there is a preferred isomer or isomeric mixture, a discussion of the  
853 material that was used in the comparative bioavailability or biowaiver study should be  
854 included and the API specification should include a test to ensure isomeric identity and purity.

855

856 If, based on the structure of the API, there is not a potential for isomerism, it is sufficient to  
857 include a statement to this effect.

858

859 *Polymorphism*

860

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

868

869 Polymorphic forms of the same chemical compound differ in internal solid-state structure  
870 and, therefore, may possess different chemical and physical properties, including packing,

871 thermodynamic, spectroscopic, kinetic, interfacial and mechanical properties. These  
872 properties can have a direct impact on API processibility, pharmaceutical product  
873 manufacturability and product quality/performance, including stability, dissolution and  
874 bioavailability. Unexpected appearance or disappearance of a polymorphic form may lead to  
875 serious pharmaceutical consequences.

876

877 Applicants to the Prequalification Programme and API manufacturers are expected to have  
878 adequate knowledge about the polymorphism of the APIs used and/or produced. Information  
879 on polymorphism can come from the scientific literature, patents, compendia or other  
880 references to determine if polymorphism is a concern, e.g. for APIs that are not *BCS highly*  
881 *soluble*. In the absence of published data for APIs that are not *BSC highly soluble*,  
882 polymorphic screening will be necessary to determine if the API can exist in more than one  
883 crystalline form. Polymorphic screening is generally accomplished via crystallization studies  
884 using different solvents and conditions.

885

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

895

896 Decision tree 4(1) of ICH Q6A can be used where screening is necessary and 4(2) can be used  
897 to investigate if different polymorphic forms have different properties that may affect  
898 performance, bioavailability and stability of the FPP and to decide whether a preferred  
899 polymorph should be monitored at release and on storage of the API. Where there is a  
900 preferred polymorph, acceptance criteria should be incorporated into the API specification to  
901 ensure polymorphic equivalence of the commercial material and that of the API batches used  
902 in the comparative bioavailability or biowaiver studies. The polymorphic characterization of  
903 the API batches used in comparative bioavailability or biowaiver studies by the above  
904 mentioned methods should be provided. The method used to control polymorphic form  
905 should be demonstrated to be specific for the preferred form.

906

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

910

- 911 • specifications for the solvent-free API in 3.2.S.2.4, if that compound is a synthetic  
912 precursor;
- 913 • specifications for the solvated API including appropriate limits on the weight ratio of  
914 API to solvent (with data to support the proposed limits);
- 915 • a description of the method used to prepare the solvate in 3.2.S.2.2.

916

917 *Particle size distribution*

918

919 For APIs that are not *BCS highly soluble* contained in solid FPPs, or liquid FPPs containing  
920 undissolved API, the particle size distribution of the material can have an effect on the in vitro  
921 and/or in vivo behaviour of the FPP. Particle size distribution can also be important in dosage

922 form performance (e.g. delivery of inhalation products), achieving uniformity of content in  
923 low-dose tablets (e.g. 2 mg or less), desired smoothness in ophthalmic preparations and  
924 stability of suspensions.

925  
926 If particle size distribution is an important parameter (e.g. as in the above cases), results from  
927 an investigation of several batches of the API should be provided, including characterization  
928 of the batch(es) used in the comparative bioavailability or biowaiver studies. API  
929 specifications should include controls on the particle size distribution to ensure consistency  
930 with the material in the batch(es) used in the comparative bioavailability and biowaiver  
931 studies (e.g. limits for d10, d50 and d90). The criteria should be established statistically based  
932 on the standard deviation of the test results from the previously mentioned studies. The  
933 following is provided for illustrative purposes as possible acceptance criteria for particle size  
934 distribution limits:

- 935
- 936 • d10 not more than (NMT) 10% of total volume less than X  $\mu\text{m}$
  - 937 • d50 XX  $\mu\text{m}$  - XXX  $\mu\text{m}$
  - 938 • d90 not less than (NLT) 90% of total volume less than XXXX  $\mu\text{m}$ .
- 939

940 Other controls on particle size distribution can be considered acceptable, if scientifically  
941 justified.

942

943 Reference documents: ICH Q6A

944

#### 945 3.2.S.3.2 *Impurities (name, manufacturer)*

946

#### 947 **Information on impurities should be provided.**

948

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

953

954 Regardless of whether a pharmacopoeial standard is claimed, a discussion should be provided  
955 of the potential and actual impurities arising from the synthesis, manufacture, or degradation  
956 of the API. This should cover starting materials, by-products, intermediates, chiral impurities  
957 and degradation products and should include the chemical names, structures and origins. The  
958 discussion of pharmacopoeial APIs should not be limited to the impurities specified in the  
959 API monograph.

960

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

966

967 The ICH thresholds for reporting, identification (used to set the limit for individual unknown  
968 impurities) and qualification are determined on the basis of potential exposure to the impurity,  
969 e.g. by the maximum daily dose (MDD) of the API. For APIs available in multiple dosage  
970 forms and strengths having different MDD values, it is imperative that the thresholds and  
971 corresponding controls for each of the presentations be considered to ensure that the risks  
972 posed by impurities have been addressed. This is normally achieved by using the *highest*

973 *potential daily MDD*, rather than the *maintenance dose*. For parenteral products, the  
974 maximum hourly dose of the API should also be included.

975  
976 It is acknowledged that APIs of semi-synthetic origin do not fall within the scope of the ICH  
977 impurity guidelines. However, depending on the nature of the API and the extent of the  
978 chemical modification steps, the *principles* on the control of impurities (e.g. reporting,  
979 identification and qualification) could also be extended to APIs of semi-synthetic origin. As  
980 an illustrative example, an API whose precursor molecule was derived from a fermentation  
981 process, or a natural product of plant or animal origin that has subsequently undergone *several*  
982 chemical modification reactions generally would fall within this scope, whereas an API whose  
983 sole chemical step was the formation of a salt from a fermentation product generally would  
984 not fall within this scope. It is understood that there is some latitude for these types of APIs.

985  
986 *Identification of impurities*

987  
988 It is recognized by the pharmacopoeias that APIs can be obtained from various sources and  
989 thus can contain impurities not considered during the development of the monograph.  
990 Furthermore, a change in the production or source may give rise to additional impurities that  
991 are not adequately controlled by the official compendial monograph. As a result, each PD is  
992 assessed independently to consider the potential impurities that may arise from the proposed  
993 route(s) of synthesis. For these reasons, the ICH limits for unspecified impurities (e.g. NMT  
994 0.10% or 1.0 mg per day intake (whichever is lower) for APIs having a maximum daily dose  
995  $\leq 2$  g/day) are generally recommended, rather than the general limits for unspecified impurities  
996 that may appear in the official compendial monograph that could potentially be higher than  
997 the applicable ICH limit.

998  
999 *Qualification of impurities*

1000  
1001 The ICH impurity guidelines should be consulted for options on the qualification of  
1002 impurities. The limit specified for an identified impurity in an *officially recognized*  
1003 *pharmacopoeia* is generally considered to be qualified. The following is an additional option  
1004 for qualification of impurities in existing APIs:

1005  
1006 The limit for an impurity present in an existing API can be accepted by comparing the  
1007 impurity results found in the existing API with those observed in an innovator product  
1008 using the same validated, stability-indicating analytical procedure (e.g. comparative  
1009 HPLC studies). If samples of the innovator product are not available, the impurity  
1010 profile may also be compared to a different prequalified FPP with the same route of  
1011 administration and similar characteristics (e.g. tablet versus capsule). It is  
1012 recommended that the studies be conducted on comparable samples (e.g. age of  
1013 samples) to obtain a meaningful comparison of the impurity profiles.

1014  
1015 Levels of impurities generated from studies under accelerated or stressed storage  
1016 conditions of the innovator or prequalified FPP are not considered  
1017 acceptable/qualified.

1018  
1019 A specified impurity present in the existing API is considered qualified if the amount  
1020 of the impurity in the existing API reflects the levels observed in the innovator or  
1021 prequalified FPP.

1022  
1023

1024 *Basis for setting the acceptance criteria*

1025

1026 The basis for setting the acceptance criteria for the impurities should be provided. This is  
1027 established by considering the identification and qualification thresholds for API-related  
1028 impurities (e.g. starting materials, by-products, intermediates, chiral impurities or degradation  
1029 products) and the concentration limits for process-related impurities (e.g. residual solvents) as  
1030 per the applicable ICH guidelines (e.g. Q3A, Q3C).

1031

1032 The qualified level should be considered as the maximum allowable limit. However, limits  
1033 which are considerably wider than the actual manufacturing process capability are  
1034 generally discouraged. For this reason, the acceptance criteria are also set taking into  
1035 consideration the actual levels of impurities found in several batches of the API from each  
1036 manufacturer, including the levels found in the batches used for the comparative  
1037 bioavailability or biowaiver studies. When reporting the results of quantitative tests, the actual  
1038 numerical results should be provided rather than vague statements such as “within limits” or  
1039 “conforms”. In the cases where a large number of batches have been tested it is acceptable to  
1040 summarize the results of the total number of batches tested with a range of analytical results.

1041

1042 If there are identified impurities specified in an official compendial monograph that are not  
1043 controlled by the proposed routine in-house analytical procedure, a justification for their  
1044 exclusion from routine analyses should be provided (e.g. “Impurities D, E and F listed in the  
1045 Ph.Int. monograph are not potential impurities from the proposed route of synthesis used by  
1046 manufacturer X”). If acceptable justification cannot be provided it should be demonstrated  
1047 that the routine in-house method is capable of separating and detecting the impurities  
1048 specified in the official compendial monograph at an acceptable level (e.g. 0.10%). If such a  
1049 demonstration cannot be performed, a one-time study should be conducted applying the  
1050 pharmacopoeial method to several recent batches to demonstrate the absence of the  
1051 pharmacopoeial listed impurities.

1052

1053 ICH class II solvent(s) used prior to the last step of the manufacturing process may be  
1054 exempted from routine control in API specifications if suitable justification is provided.  
1055 Submission of results demonstrating less than 10% of the ICH Q3C limit (option I) of the  
1056 solvent(s) in three consecutive production-scale batches or six consecutive pilot-scale batches  
1057 of the API or a suitable intermediate would be considered acceptable justification. The last  
1058 step solvents used in the process should always be routinely controlled in the final API.

1059

1060 For guidance on acceptable residual solvent limits, refer to ICH Q3C. The limit for residues  
1061 of triethylamine (TEA) is either 320 ppm on the basis of ICH Q3C option I or 3.2 mg/day on  
1062 the basis of permitted daily exposure (PDE).

1063

1064 The absence of known established highly toxic impurities (genotoxic) used in the process or  
1065 formed as a by-product should be discussed and suitable limits should be proposed. The limits  
1066 should be justified by appropriate reference to available guidances (e.g.  
1067 EMEA/CHMP/QWP/251344/2006 or USFDA Guidance for Industry: Genotoxic and  
1068 carcinogenic impurities in drug substances and products, recommended approaches,  
1069 December 2008) or by providing experimental safety data or published data in peer-reviewed  
1070 journals.

1071

1072 Residues of metal catalysts used in the manufacturing process and determined to be present in  
1073 batches of API are to be controlled in specifications. This requirement does not apply to  
1074 metals that are deliberate components of the pharmaceutical substance (such as a counter ion

1075 of a salt) or metals that are used as a pharmaceutical excipient in the FPP (e.g. an iron oxide  
1076 pigment). The guideline on the specification limits for residues of metal catalysts or metal  
1077 reagents EMEA/CHMP/SWP/4446/2000 or any equivalent approaches can be used to address  
1078 this issue. The requirement normally does not apply to extraneous metal contaminants that are  
1079 more appropriately addressed by GMP, GDP or any other relevant quality provision such as  
1080 the heavy metal test in monographs of recognized pharmacopoeias that cover metal  
1081 contamination originating from manufacturing equipment and the environment.

1082  
1083 Reference documents: ICH Q3A, Q3C, Q6A

### 1084 1085 **3.2.S.4 Control of the API (name, manufacturer)**

#### 1086 1087 **3.2.S.4.1 Specification (name, manufacturer)**

1088  
1089 **The specification for the API should be provided.**

1090  
1091 As defined in ICH's Q6A guideline, a specification is:

1092  
1093 *“a list of tests, references to analytical procedures and appropriate acceptance*  
1094 *criteria, which are numerical limits, ranges, or other criteria for the tests described. It*  
1095 *establishes the set of criteria to which an API or FPP should conform to be*  
1096 *considered acceptable for its intended use. “Conformance to specifications” means*  
1097 *that the API and / or FPP, when tested according to the listed analytical procedures,*  
1098 *will meet the listed acceptance criteria. Specifications are critical quality standards*  
1099 *that are proposed and justified by the manufacturer and approved by regulatory*  
1100 *authorities.”*

1101  
1102 Copies of the API specifications, dated and signed by authorized personnel (e.g. the person in  
1103 charge of the quality control or quality assurance department) should be provided in the PD,  
1104 including specifications from each API manufacturer as well as those of the FPP  
1105 manufacturer.

1106  
1107 The FPP manufacturer's API specification should be summarized according to the table in the  
1108 QOS-PD template under the headings tests, acceptance criteria and analytical procedures  
1109 (including types, sources and versions for the methods).

- 1110  
1111
- 1112 • The *standard* declared by the applicant could be an officially recognized compendial  
1113 standard (e.g. Ph.Int., Ph.Eur., BP, USP) or a House (manufacturer's) standard.
  - 1114 • The *specification reference number and version* (e.g. *revision number and/or date*)  
1115 should be provided for version control purposes.
  - 1116 • For the analytical procedures, the *type* should indicate the kind of analytical procedure  
1117 used (e.g. visual, IR, UV, HPLC, laser diffraction), the *source* refers to the origin of  
1118 the analytical procedure (e.g. Ph.Int., Ph.Eur., BP, USP, in-house) and the *version* (e.g.  
1119 *code number/version/date*) should be provided for version control purposes.

1120 In cases where there is more than one API manufacturer, the FPP manufacturer's API  
1121 specifications should be one single compiled set of specifications that is identical for each  
1122 manufacturer. It is acceptable to lay down in the specification more than one acceptance  
1123 criterion and/or analytical method for a single parameter with the statement “for API from  
1124 manufacturer A” (e.g. in the case of residual solvents).

1125

1126 Any non routine testing should be clearly identified as such and justified along with the  
1127 proposal on the frequency of non routine testing.

1128  
1129 The ICH Q6A guideline outlines recommendations for a number of *universal* and *specific*  
1130 *tests* and criteria for APIs.

1131  
1132 Reference documents: ICH Q3A, Q3C, Q6A, *officially recognized pharmacopoeia*

1133  
1134 **3.2.S.4.2 Analytical procedures (name, manufacturer)**

1135  
1136 **The analytical procedures used for testing the API should be provided.**

1137  
1138 Copies of the in-house analytical procedures used to generate testing results provided in the  
1139 PD, as well as those proposed for routine testing of the API by the FPP manufacturer, should  
1140 be provided. Unless modified, it is not necessary to provide copies of officially recognized  
1141 compendial analytical procedures.

1142  
1143 Tables for summarizing a number of the different analytical procedures and validation  
1144 information (e.g. HPLC assay/impurity methods, GC methods) can be found in the 2.3.R  
1145 Regional information section of the QOS-PD (i.e. 2.3.R.2). These tables should be used to  
1146 summarize the in-house analytical procedures *of the FPP manufacturer* for determination of  
1147 the residual solvents, assay and purity of the API, in section 2.3.S.4.2 of the QOS-PD. Other  
1148 methods used to generate assay and purity data in the PD can be summarized in 2.3.S.4.4 (c)  
1149 or 2.3.S.7.3 (b) of the QOS-PD. Officially recognized compendial methods need not be  
1150 summarized unless modifications have been made.

1151  
1152 Although HPLC is normally considered the method of choice for determining API-related  
1153 impurities, other chromatographic methods such as GC and TLC can also be used, if  
1154 appropriately validated. For determination of related substances, reference standards should  
1155 normally be available for each of the identified impurities, particularly those known to be  
1156 toxic and the concentration of the impurities should be quantitated against their own reference  
1157 standards. Impurity standards may be obtained from pharmacopoeias (individual impurities  
1158 or resolution mixtures), from commercial sources or prepared in-house. It is considered  
1159 acceptable to use the API as an external standard to estimate the levels of impurities, provided  
1160 the response factors of those impurities are sufficiently close to that of the API, i.e. between  
1161 80 and 120%. In cases where the response factor is outside this range, it may still be  
1162 acceptable to use the API, provided a correction factor is applied. Data to support calculation  
1163 of the correction factor should be provided for an in-house method. Unspecified impurities  
1164 may be quantitated using a solution of the API as the reference standard at a concentration  
1165 corresponding to the limit established for individual unspecified impurities (e.g. 0.10%). The  
1166 test for related substances in the Ph.Int. monograph for Lamivudine serves as a typical  
1167 example.

1168  
1169 The system suitability tests (SSTs) represent an integral part of the method and are used to  
1170 ensure the adequate performance of the chosen chromatographic system. As a minimum,  
1171 HPLC and GC purity methods should include SSTs for resolution and repeatability. For  
1172 HPLC methods to control API-related impurities, this is typically done using a solution of the  
1173 API with a concentration corresponding to the limit for unspecified impurities. Resolution of  
1174 the two closest eluting peaks is generally recommended. However, the choice of alternate  
1175 peaks can be used if justified (e.g. choice of a toxic impurity). In accordance with the Ph.Int.  
1176 section on *Methods of Analysis*, the repeatability test should include an acceptable number of

1177 replicate injections. HPLC assay methods should include SSTs for repeatability and in  
1178 addition either peak asymmetry, theoretical plates or resolution. For TLC methods, the SSTs  
1179 should verify the ability of the system to separate and detect the analyte(s) (e.g. by applying a  
1180 spot corresponding to the API at a concentration corresponding to the limit of unspecified  
1181 impurities).

1182  
1183 Reference documents: ICH Q2, WHO Technical Report Series, No. 943, Annex 3

1184  
1185 **3.2.S.4.3      *Validation of analytical procedures (name, manufacturer)***

1186  
1187 **Analytical validation information, including experimental data for the analytical**  
1188 **procedures used for testing the API, should be provided.**

1189  
1190 Copies of the validation reports for the analytical procedures used to generate testing results  
1191 provided in the PD, as well as those proposed for routine testing of the API by the FPP  
1192 manufacturer, should be provided.

1193  
1194 Tables for summarizing a number of the different analytical procedures and validation  
1195 information (e.g. HPLC assay/impurity methods, GC methods) can be found in the 2.3.R  
1196 Regional information section of the QOS-PD (i.e. 2.3.R.2). These tables should be used to  
1197 summarize the validation information of the analytical procedures *of the FPP manufacturer*  
1198 for determination of residual solvents, assay and purity of the API, in section 2.3.S.4.3 of the  
1199 QOS-PD. The validation data for other methods used to generate assay and purity data in the  
1200 PD can be summarized in 2.3.S.4.4 (c) or 2.3.S.7.3 (b) of the QOS-PD.

1201  
1202 As recognized by regulatory authorities and pharmacopoeias themselves, verification of  
1203 compendial methods can be necessary. The compendial methods as published are typically  
1204 validated based on an API or an FPP originating from a specific manufacturer. Different  
1205 sources of the same API or FPP can contain impurities and/or degradation products that were  
1206 not considered during the development of the monograph. Therefore the monograph and  
1207 compendial method should be demonstrated suitable to control the impurity profile of the API  
1208 from the intended source(s).

1209  
1210 In general verification is not necessary for compendial API *assay* methods. However,  
1211 specificity of a specific compendial assay method should be demonstrated if there are any  
1212 potential impurities that are not specified in the compendial monograph. If an officially  
1213 recognized compendial method is used to control API-related impurities that are not specified  
1214 in the monograph, full validation of the method is expected with respect to those impurities.

1215  
1216 If an officially recognized compendial standard is claimed and an in-house method is used in  
1217 lieu of the compendial method (e.g. for assay or for specified impurities), equivalency of the  
1218 in-house and compendial methods should be demonstrated. This could be accomplished by  
1219 performing duplicate analyses of one sample by both methods and providing the results from  
1220 the study. For impurity methods, the sample analyzed should be the API spiked with  
1221 impurities at concentrations equivalent to their specification limits.

1222  
1223 Reference documents: ICH Q2

1224  
1225 **3.2.S.4.4      *Batch analyses (name, manufacturer)***

1226  
1227 **Description of batches and results of batch analyses should be provided.**

1228

1229 The information provided should include batch number, batch size, date and production site of  
1230 relevant API batches used in comparative bioavailability or biowaiver studies, stability, pilot,  
1231 scale-up and, if available, production-scale batches. This data is used to establish the  
1232 specifications and evaluate consistency in API quality.

1233

1234 Analytical results should be provided from at least two batches of at least pilot scale from  
1235 each proposed manufacturing site of the API and should include the batch(es) used in the  
1236 comparative bioavailability or biowaiver studies. A pilot-scale batch should be manufactured  
1237 by a procedure fully representative of and simulating that to be applied to a full production-  
1238 scale batch.

1239

1240 Copies of the certificates of analysis, both from the API manufacturer(s) and the FPP  
1241 manufacturer, should be provided for the profiled batches and any company responsible for  
1242 generating the test results should be identified. The FPP manufacturer's test results should be  
1243 summarized in the QOS-PD.

1244

1245 The discussion of results should focus on observations noted for the various tests, rather than  
1246 reporting comments such as "all tests meet specifications". For quantitative tests (e.g.  
1247 individual and total impurity tests and assay tests), it should be ensured that actual *numerical*  
1248 *results* are provided rather than vague statements such as "within limits" or "conforms".

1249

1250 A discussion and justification should be provided for any incomplete analyses (e.g. results not  
1251 tested according to the proposed specification).

1252

1253 Reference documents: ICH Q3A, Q3C, Q6A

1254

#### 1255 **3.2.S.4.5** *Justification of specification (name, manufacturer)*

1256

1257 **Justification for the API specification should be provided.**

1258

1259 A discussion should be provided on the inclusion of certain tests, evolution of tests, analytical  
1260 procedures and acceptance criteria, differences from the officially recognized compendial  
1261 standard(s), etc. If the officially recognized compendial methods have been modified or  
1262 replaced, a discussion should be included.

1263

1264 The justification for certain tests, analytical procedures and acceptance criteria may have been  
1265 discussed in other sections of the PD (e.g. impurities, particle size distribution) and does not  
1266 need to be repeated here, although a cross-reference to their location should be provided.

1267

1268 Reference documents: ICH Q3A, Q3C, Q6A, *officially recognized pharmacopoeia*

1269

#### 1270 **3.2.S.5** *Reference standards or materials (name, manufacturer)*

1271

1272 **Information on the reference standards or reference materials used for testing of the**  
1273 **API should be provided.**

1274

1275 Information should be provided on the reference standard(s) used to generate data in the PD,  
1276 as well as those to be used by the FPP manufacturer in routine API and FPP testing.

1277

1278 The source(s) of the reference standards or materials used in the testing of the API should be  
1279 provided (e.g. those used for the identification, purity, assay tests). These could be classified  
1280 as *primary* or *secondary* reference standards.

1281  
1282 A suitable primary reference standard should be obtained from an officially recognized  
1283 pharmacopoeial source (e.g. Ph.Int., Ph.Eur., BP, USP) where one exists and the lot number  
1284 should be provided. Where a pharmacopoeial standard is claimed for the API and/or the FPP,  
1285 the primary reference standard should be obtained from that pharmacopoeia when available.  
1286 Primary reference standards from officially recognized pharmacopoeial sources do not need  
1287 further structural elucidation.

1288  
1289 Otherwise, a primary standard may be a batch of the API that has been fully characterized  
1290 (e.g. by IR, UV, NMR, MS analyses). Further purification techniques may be needed to  
1291 render the material acceptable for use as a chemical reference standard. The purity  
1292 requirements for a chemical reference substance depend upon its intended use. A chemical  
1293 reference substance proposed for an identification test does not require meticulous  
1294 purification, since the presence of a small percentage of impurities in the substance often has  
1295 no noticeable effect on the test. On the other hand, chemical reference substances that are to  
1296 be used in assays should possess a high degree of purity (such as 99.5% on the dried or  
1297 water/solvent free basis). Absolute content of the primary reference standard must be declared  
1298 and should follow the scheme: 100% minus organic impurities (quantitated by an assay  
1299 procedure, e.g. HPLC, DSC, etc.) minus inorganic impurities minus volatile impurities by loss  
1300 on drying (or water content minus residual solvents).

1301  
1302 A secondary (or in-house) reference standard can be used by establishing it against a suitable  
1303 primary reference standard, e.g. by providing legible copies of the IR of the primary and  
1304 secondary reference standards run concomitantly and by providing its certificate of analysis,  
1305 including assay determined against the primary reference standard. A secondary reference  
1306 standard is often characterized and evaluated for its intended purpose with additional  
1307 procedures other than those used in routine testing (e.g. if additional solvents are used during  
1308 the additional purification process that are not used for routine purposes).

1309  
1310 Reference standards should normally be established for specified impurities. Refer to  
1311 3.2.S.4.2 for additional guidance.

1312  
1313 Reference documents: ICH Q6A, WHO Technical Report Series, No. 943, Annex 3

### 1314 1315 **3.2.S.6 Container closure system (name, manufacturer)**

1316  
1317 **A description of the container closure system(s) should be provided, including the**  
1318 **identity of materials of construction of each primary packaging component, and their**  
1319 **specifications. The specifications should include description and identification (and**  
1320 **critical dimensions with drawings, where appropriate). Non-compendial methods (with**  
1321 **validation) should be included, where appropriate.**

1322  
1323 **For non-functional secondary packaging components (e.g. those that do not provide**  
1324 **additional protection), only a brief description should be provided. For functional**  
1325 **secondary packaging components, additional information should be provided.**

1326  
1327 **The suitability should be discussed with respect to, for example, choice of materials,**  
1328 **protection from moisture and light, compatibility of the materials of construction with**

1329 **the API, including sorption to container and leaching, and/or safety of materials of**  
1330 **construction.**

1331

1332 The WHO *Guidelines on packaging for pharmaceutical products* (WHO Technical Report  
1333 Series, No. 902, Annex 9, 2002) and the officially recognized pharmacopoeias should be  
1334 consulted for recommendations on the packaging information for APIs.

1335

1336 Primary packaging components are those that are in direct contact with the API or FPP. The  
1337 specifications for the primary packaging components should be provided and should include a  
1338 specific test for identification (e.g. IR).

1339

1340 Copies of the labels applied on the secondary packaging of the API should be provided and  
1341 should include the conditions of storage. In addition, the name and address of the  
1342 manufacturer of the API should be stated on the container, regardless of whether relabeling is  
1343 conducted at any stage during the API distribution process.

1344

1345 **3.2.S.7 Stability (name, manufacturer)**

1346

1347 **3.2.S.7.1 Stability summary and conclusions (name, manufacturer)**

1348

1349 **The types of studies conducted, protocols used, and the results of the studies should be**  
1350 **summarised. The summary should include results, for example, from forced**  
1351 **degradation studies and stress conditions, as well as conclusions with respect to storage**  
1352 **conditions and re-test date or shelf-life, as appropriate.**

1353

1354 The WHO guideline *Stability testing of active pharmaceutical ingredients and finished*  
1355 *pharmaceutical products* (WHO Technical Report Series, No. 953, Annex 2) should be  
1356 consulted for recommendations on the core stability data package required for the  
1357 prequalification of APIs and FPPs.

1358

1359 As outlined in the WHO stability guideline, the purpose of stability testing is to:

1360

1361 *“provide evidence of how the quality of an API or FPP varies with time under the*  
1362 *influence of a variety of environmental factors such as temperature, humidity and*  
1363 *light.”*

1364

1365 The tables in the QOS-PD template should be used to summarize the results from the stability  
1366 studies and related information (e.g. conditions, testing parameters, conclusions,  
1367 commitments).

1368

1369 *Stress testing*

1370

1371 As outlined in the ICH Q1A guidance document, stress testing of the API can help identify  
1372 the likely degradation products, which can in turn help establish the degradation pathways and  
1373 the intrinsic stability of the molecule and validate the stability indicating power of the  
1374 analytical procedures used. The nature of the stress testing will depend on the individual API  
1375 and the type of FPP involved.

1376

1377 Stress testing may be carried out on a single batch of the API. For examples of typical stress  
1378 conditions refer to WHO Technical Report Series, No. 953, Annex 2, Section 2.1.2, as well

1379 as, “A typical set of studies of the degradation paths of an active pharmaceutical ingredient”  
1380 in WHO Technical Report Series, No. 929, Annex 5, Table A.1.

1381  
1382 The objective of stress testing is not to completely degrade the API, but to cause degradation  
1383 to occur to a small extent, typically 10-30% loss of active by assay when compared with non-  
1384 degraded API. This target is chosen so that some degradation occurs, but not enough to  
1385 generate secondary products. For this reason, the conditions and duration may need to be  
1386 varied when the API is especially susceptible to a particular stress factor. In the total absence  
1387 of degradation products after 10 days, the API is considered stable under the particular stress  
1388 condition.

1389  
1390 The tables in the QOS-PD template should be used to summarize the results of the stress  
1391 testing and should include the treatment conditions (e.g. temperatures, relative humidities,  
1392 concentrations of solutions, durations) and the observations for the various test parameters  
1393 (e.g. assay, degradation products). The discussion of results should highlight whether mass  
1394 balance was observed.

1395  
1396 Photostability testing should be an integral part of stress testing. The standard conditions are  
1397 described in ICH Q1B. If “protect from light” is stated in one of the officially recognized  
1398 pharmacopoeia for the API, it is sufficient to state “protect from light” on labelling, in lieu of  
1399 photostability studies, when the container closure system is shown to be light protective.

1400  
1401 When available, it is acceptable to provide the relevant data published in the scientific  
1402 literature (inter alia WHOPARs, EPARs) to support the identified degradation products and  
1403 pathways.

1404  
1405 *Accelerated and long-term testing*

1406  
1407 Available information on the stability of the API under accelerated and long-term conditions  
1408 should be provided, including information in the public domain or obtained from scientific  
1409 literature. The source of the information should be identified.

1410  
1411 The required long-term storage conditions for APIs in the Prequalification Programme is  
1412 either  $30^{\circ}\text{C}\pm 2^{\circ}\text{C}/65\%\pm 5\%\text{RH}$  or  $30^{\circ}\text{C}\pm 2^{\circ}\text{C}/75\%\pm 5\%\text{RH}$ . Studies covering the proposed re-  
1413 test period at the above mentioned long-term storage conditions will provide better assurance  
1414 of the stability of APIs at the conditions of the supply chain corresponding to the WHO and  
1415 Prequalification Programme environments. Alternative conditions should be supported with  
1416 appropriate evidence, which may include literature references or in-house studies,  
1417 demonstrating that storage at  $30^{\circ}\text{C}$  is inappropriate for the API. For APIs intended for storage  
1418 in a refrigerator and those intended for storage in a freezer refer to the WHO stability  
1419 guideline WHO Technical Report Series, No. 953 Annex 2. APIs intended for storage below  
1420  $-20^{\circ}\text{C}$  should be treated on a case-by-case basis.

1421  
1422 To establish the re-test period, data should be provided on not less than three batches of at  
1423 least pilot scale. The batches should be manufactured by the same synthesis route as  
1424 production batches and using a method of manufacture and procedure that simulates the final  
1425 process to be used for production batches. The stability testing programme should be  
1426 summarized and the results of stability testing should be summarized in the dossier and in the  
1427 tables in the QOS-PD.

1428

1429 The information on the stability studies should include details such as storage conditions,  
1430 batch number, batch size, container closure system and completed (and proposed) test  
1431 intervals. The discussion of results should focus on observations noted for the various tests,  
1432 rather than reporting comments such as “all tests meet specifications”. Ranges of analytical  
1433 results where relevant and any trends that were observed should be included. For quantitative  
1434 tests (e.g. individual and total degradation product tests and assay tests), it should be ensured  
1435 that actual numerical results are provided rather than vague statements such as “within limits”  
1436 or “conforms”. Where different from the methods described in S.4.2, descriptions and  
1437 validation of the methodology used in stability studies should be provided.

1438  
1439 The minimum data required at the time of submitting the dossier (in the general case):  
1440

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

1441 \*Where long-term conditions are 30°C±2°C/65%±5%RH or 30°C±2°C/75%±5%RH, there is  
1442 no intermediate condition.

1443  
1444 Refer to WHO Technical Report Series, No. 953, Annex 2 for further information regarding  
1445 the storage conditions, container closure system, test specifications and testing frequency.

1446  
1447 *Proposed storage statement and re-test period*

1448  
1449 A storage statement should be established for display on the label based on the stability  
1450 evaluation of the API. The WHO stability guideline includes a number of recommended  
1451 storage statements that should be used, when supported by the stability studies.

1452  
1453 A re-test period should be derived from the stability information and should be displayed on  
1454 the container label.

1455  
1456 After this re-test period, a batch of API destined for use in the manufacture of an FPP could  
1457 be re-tested and then, if in compliance with the specification, could be used immediately (e.g.  
1458 within 30 days). If re-tested and found compliant, the batch does *not* receive an additional  
1459 period corresponding to the time established for the re-test period. However, an API batch  
1460 can be re-tested multiple times and a different portion of the batch used after each re-test, as  
1461 long as it continues to comply with the specification. For APIs known to be labile (e.g.  
1462 certain antibiotics), it is more appropriate to establish a shelf-life rather than a re-test period  
1463 (reference: ICH Q1A).

1464  
1465 Limited extrapolation of the real time data from the long-term storage condition beyond the  
1466 observed range to extend the re-test period can be undertaken at the time of assessment of the  
1467 PD, if justified. Applicants should consult the ICH Q1E guideline for further details on the  
1468 evaluation and extrapolation of results from stability data (e.g. if significant change was not  
1469 observed within 6 months at accelerated condition and the data show little or no variability,  
1470 the proposed re-test period could be up to two times the period covered by the long-term data,  
1471 but should not exceed the long-term data by 12 months).

1472  
1473 Reference documents: ICH Q1A, Q1B, Q1D, Q1E, WHO Technical Report Series, No. 953,  
1474 Annex 2

1475

1476 **3.2.S.7.2** *Post-approval stability protocol and stability commitment*  
1477 *(name, manufacturer)*

1478

1479 **The post-approval stability protocol and stability commitment should be provided.**

1480

1481 *Primary stability study commitment*

1482

1483 When available long-term stability data on primary batches do not cover the proposed re-test  
1484 period granted at the time of assessment of the PD, a commitment should be made to continue  
1485 the stability studies in order to firmly establish the re-test period. A written commitment  
1486 (signed and dated) to continue long-term testing over the re-test period should be included in  
1487 the dossier when relevant.

1488

1489 *Commitment stability studies*

1490

1491 The long-term stability studies for the *commitment batches* should be conducted through the  
1492 proposed re-test period on at least three production batches. Where stability data was not  
1493 provided for three production batches, a written commitment (signed and dated) should be  
1494 included in the dossier.

1495

1496 The stability protocol for the *commitment batches* should be provided and should include, but  
1497 not be limited to, the following parameters:

1498

- 1499 • number of batch(es) and different batch sizes, if applicable;
- 1500 • relevant physical, chemical, microbiological and biological test methods;
- 1501 • acceptance criteria;
- 1502 • reference to test methods;
- 1503 • description of the container closure system(s);
- 1504 • testing frequency;
- 1505 • description of the conditions of storage (standardized conditions for long-term testing  
1506 as described in these guidelines and consistent with the API labelling, should be used);  
1507 and
- 1508 • other applicable parameters specific to the API.

1509

1510 *Ongoing stability studies*

1511

1512 The stability of the API should be monitored according to a continuous and appropriate  
1513 programme that will permit the detection of any stability issue (e.g. changes in levels of  
1514 degradation products). The purpose of the ongoing stability programme is to monitor the API  
1515 and to determine that the API remains and can be expected to remain within the re-test period  
1516 in all future batches.

1517

1518 At least one production batch per year of API (unless none is produced during that year)  
1519 should be added to the stability monitoring programme and tested at least annually to confirm  
1520 the stability. In certain situations, additional batches should be included. A written  
1521 commitment (signed and dated) for ongoing stability studies should be included in the dossier.

1522

1523 Refer to WHO Technical Report Series, No. 953, Annex 2, Section 2.1.11 for further  
1524 information on ongoing stability studies.

1525  
1526 Any differences in the stability protocols used for the primary batches and those proposed for  
1527 the *commitment batches* or *ongoing batches* should be scientifically justified.  
1528

1529 Reference documents: ICH Q1A, Q1B, Q1D, Q1E, WHO Technical Report Series, No. 953,  
1530 Annex 2

1531  
1532 **3.2.S.7.3 Stability data (name, manufacturer)**  
1533

1534 **Results of the stability studies (e.g. forced degradation studies and stress conditions)**  
1535 **should be presented in an appropriate format such as tabular, graphical, or narrative.**  
1536 **Information on the analytical procedures used to generate the data and validation of**  
1537 **these procedures should be included.**  
1538

1539 The actual stability results used to support the proposed re-test period should be included in  
1540 the dossier. For quantitative tests (e.g. individual and total degradation product tests and assay  
1541 tests), it should be ensured that actual numerical results are provided rather than vague  
1542 statements such as “within limits” or “conforms”.

1543  
1544 Reference documents: ICH Q1A, Q1B, Q1D, Q1E, Q2, WHO Technical Report Series, No.  
1545 953, Annex 2

1546  
1547 **3.2.P Drug product (or finished pharmaceutical product (FPP)) (name, dosage form)**  
1548

1549 **3.2.P.1 Description and composition of the FPP (name, dosage form)**  
1550

1551 **A description of the FPP and its composition should be provided. The information**  
1552 **provided should include, for example:**  
1553

- **Description of the dosage form**

1554  
1555 The description of the FPP should include the physical description, available strengths,  
1556 release mechanism (e.g. immediate, modified (delayed or extended)), as well as any  
1557 other distinguishable characteristics, e.g.:

1558  
1559 “The proposed XYZ 50mg Tablets are available as white, oval, film-coated tablets,  
1560 debossed with ‘50’ on one side and a break-line on the other side.  
1561

1562 The proposed XYZ 100mg Tablets are available as yellow, round, film-coated tablets,  
1563 debossed with ‘100’ on one side and plain on the other side.”  
1564

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

1565  
1566 The tables in the QOS-PD template should be used to summarize the composition of  
1567 the FPP and express the quantity of each component on a per unit basis (e.g. mg per  
1568 tablet, mg per ml, mg per vial) and percentage basis, including a statement of the total  
1569 weight or measure of the dosage unit. The individual components for mixtures  
1570 prepared in-house (e.g. coatings) should be included in the tables, where applicable.  
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*All components* used in the manufacturing process should be included, including those that may not be added to every batch (e.g. acid and alkali), those that may be removed during processing (e.g. solvents) and any others (e.g. nitrogen, silicon for stoppers). If the FPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g. “1 mg of active ingredient base = 1.075 mg active ingredient hydrochloride”). All overages should be clearly indicated (e.g. “contains 2% overage of the API to compensate for manufacturing losses”).

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

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

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

- **Description of accompanying reconstitution diluent(s)**

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

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

- **Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable**

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

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

Reference documents: ICH Q6A

1626 **3.2.P.2 Pharmaceutical development (name, dosage form)**

1627

1628 **The Pharmaceutical development section should contain information on the**  
1629 **development studies conducted to establish that the dosage form, the formulation,**  
1630 **manufacturing process, container closure system, microbiological attributes and usage**  
1631 **instructions are appropriate for the purpose specified in the product dossier. The studies**  
1632 **described here are distinguished from routine control tests conducted according to**  
1633 **specifications. Additionally, this section should identify and describe the formulation**  
1634 **and process attributes (critical parameters) that can influence batch reproducibility,**  
1635 **product performance and FPP quality. Supportive data and results from specific studies**  
1636 **or published literature can be included within or attached to the Pharmaceutical**  
1637 **development section. Additional supportive data can be referenced to the relevant**  
1638 **nonclinical or clinical sections of the product dossier.**

1639

1640 Reference documents: ICH Q6A, Q8, Q9, Q10

1641

1642 **3.2.P.2.1 Components of the FPP (name, dosage form)**

1643

1644 **3.2.P.2.1.1 Active pharmaceutical ingredient (name, dosage form)**

1645

1646 **The compatibility of the API with excipients listed in 3.2.P.1 should be discussed.**  
1647 **Additionally, key physicochemical characteristics (e.g. water content, solubility,**  
1648 **particle size distribution, polymorphic or solid state form) of the API that can**  
1649 **influence the performance of the FPP should be discussed. For fixed-dose**  
1650 **combinations, the compatibility of APIs with each other should be discussed.**

1651

1652 Physicochemical characteristics of the API may influence both the manufacturing  
1653 capability and the performance of the FPP.

1654

1655 Guidance on compatibility studies is provided in Appendix 3 of the WHO *Guidelines*  
1656 *for registration of fixed-dose combination medicinal products* (WHO Technical  
1657 Report Series, No. 929, Annex 5, 2005). In addition to visual examination,  
1658 chromatographic results (assay, purity) are required to demonstrate API-API and API-  
1659 excipient compatibility. In general, API-excipient compatibility is not required to be  
1660 established for specific excipients when evidence is provided (e.g. SmPC or product  
1661 leaflet) that the excipients are present in the comparator product.

1662

1663 **3.2.P.2.1.2 Excipients (name, dosage form)**

1664

1665 **The choice of excipients listed in 3.2.P.1, their concentration, their characteristics**  
1666 **that can influence the FPP performance should be discussed relative to their**  
1667 **respective functions.**

1668

1669 Ranges or alternates for excipients are normally not accepted, unless supported by  
1670 appropriate process validation data. Where relevant, compatibility study results (e.g.  
1671 compatibility of a primary or secondary amine API with lactose) should be included to  
1672 justify the choice of excipients. Specific details should be provided where necessary  
1673 (e.g. use of potato or corn starch).

1674

1675 Where antioxidants are included in the formulation, the effectiveness of the proposed  
1676 concentration of the antioxidant should be justified and verified by appropriate studies.

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Antimicrobial preservatives are discussed in 3.2.P.2.5.

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

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

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

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

When assessing the data requirements needed for multiple strengths, WHO reference documents (e.g. WHO Technical Report Series, No. 937, Annex 7) should be consulted.

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

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

1728 *In vitro dissolution or drug release*

1729

1730 A discussion should be included as to how the development of the formulation relates  
1731 to development of the dissolution method(s) and the generation of the dissolution  
1732 profile.

1733

1734 The results of studies justifying the choice of in vitro dissolution or drug release  
1735 conditions (e.g. apparatus, rotation speed, medium) should be provided. Data should  
1736 also be submitted to demonstrate whether the method is sensitive to changes in  
1737 manufacturing processes and/or changes in grades and/or amounts of critical  
1738 excipients and particle size where relevant. The dissolution method should be sensitive  
1739 to any changes in the product that would result in a change in one or more of the  
1740 pharmacokinetic parameters. Use of a single point test or a dissolution range should be  
1741 justified based on the solubility and/or biopharmaceutical classification of the API.

1742

1743 For slower dissolving immediate-release products (e.g. Q=80% in 90 minutes), a  
1744 second time point may be warranted (e.g. Q=60% in 45 minutes).

1745

1746 Modified-release FPPs should have a meaningful in vitro release rate (dissolution) test  
1747 that is used for routine quality control. Preferably this test should possess in vitro-in  
1748 vivo correlation. Results demonstrating the effect of pH on the dissolution profile  
1749 should be submitted if appropriate for the type of dosage form.

1750

1751 For extended-release FPPs, the testing conditions should be set to cover the entire time  
1752 period of expected release (e.g. at least three test intervals chosen for a 12-hour release  
1753 and additional test intervals for longer duration of release). One of the test points  
1754 should be at the early stage of drug release (e.g. within the first hour) to demonstrate  
1755 absence of dose dumping. At each test period, upper and lower limits should be set for  
1756 individual units. Generally, the acceptance range at each intermediate test point should  
1757 not exceed 25% or  $\pm 12.5\%$  of the targeted value. Dissolution results should be  
1758 submitted for several lots, including those lots used for pharmacokinetic and  
1759 bioavailability or biowaiver studies.

1760

1761 Recommendations for conducting and assessing comparative dissolution profiles can  
1762 be found in Appendix 1.

1763

1764 **3.2.P.2.2.2 Overages (name, dosage form)**

1765

1766 **Any overages in the formulation(s) described in 3.2.P.1 should be justified.**

1767

1768 Justification of an overage to compensate for loss during manufacture should be  
1769 provided, including the step(s) where the loss occurs, the reasons for the loss and  
1770 batch analysis release data (assay results).

1771

1772 Overages for the sole purpose of extending the shelf-life of the FPP are generally not  
1773 acceptable.

1774

1775 **3.2.P.2.2.3 Physicochemical and biological properties (name, dosage form)**

1776

1777 **Parameters relevant to the performance of the FPP, such as pH, ionic strength,  
1778 dissolution, redispersion, reconstitution, particle size distribution, aggregation,**

1779 **polymorphism, rheological properties, biological activity or potency, and/or**  
1780 **immunological activity, should be addressed.**

1781

1782 In addition to the above considerations, refractive index may be a relevant parameter  
1783 for some FPPs.

1784

1785 **3.2.P.2.3 Manufacturing process development (name, dosage form)**

1786

1787 **The selection and optimization of the manufacturing process described in 3.2.P.3.3, in**  
1788 **particular its critical aspects, should be explained. Where relevant, the method of**  
1789 **sterilisation should be explained and justified.**

1790

1791 Where relevant, justification for the selection of aseptic processing or other sterilization  
1792 methods over terminal sterilization should be provided.

1793

1794 **Differences between the manufacturing process(es) used to produce comparative**  
1795 **bioavailability or biowaiver batches and the process described in 3.2.P.3.3 that can**  
1796 **influence the performance of the product should be discussed.**

1797

1798 For products that meet the criteria of an *established multisource product*, in order to fulfil the  
1799 requirements of section P.2.3, section P.2.3 (b) of the dossier and QOS-PD should be  
1800 completed and a product quality review should be submitted as outlined in Appendix 2. The  
1801 guidance that follows applies to all other products, for which section P.2.3 should be  
1802 completed in its entirety.

1803

1804 The rationale for choosing the particular pharmaceutical product should be provided. The  
1805 scientific rationale for the choice of the manufacturing, filling and packaging processes that  
1806 can influence FPP quality and performance should be explained (e.g. wet granulation using  
1807 high shear granulator). API stress study results may be included in the rationale. Any  
1808 developmental work undertaken to protect the FPP from deterioration should also be included  
1809 (e.g. protection from light or moisture).

1810

1811 The scientific rationale for the selection, optimization and scale-up of the manufacturing  
1812 process described in 3.2.P.3.3 should be explained, in particular the critical aspects (e.g. rate  
1813 of addition of granulating fluid, massing time, granulation end-point). The equipment should  
1814 be identified by type and working capacity.

1815

1816 **3.2.P.2.4 Container closure system (name, dosage form)**

1817

1818 **The suitability of the container closure system (described in 3.2.P.7) used for the storage,**  
1819 **transportation (shipping) and use of the FPP should be discussed. This discussion should**  
1820 **consider, e.g. choice of materials, protection from moisture and light, compatibility of**  
1821 **the materials of construction with the dosage form (including sorption to container and**  
1822 **leaching) safety of materials of construction, and performance (such as reproducibility**  
1823 **of the dose delivery from the device when presented as part of the FPP).**

1824

1825 The information on suitability of the container closure system depends on the dosage form  
1826 and route of administration. The following table outlines the general recommendations for  
1827 the various dosage forms for one-time studies to establish the suitability of the container  
1828 closure system.

1829

1830  
1831

	<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)
USP <661> Containers – plastics	X	X	X (includes USP <87>/<88> tests)
USP <671> Containers – performance testing	X	X	X
USP <381> Elastomeric closures for injections	---	---	X (includes USP <87>/<88> tests)

1832 \*e.g. coating of tubes, siliconization of rubber stoppers, sulfur treatment of ampoules/vials  
1833 X = information should be submitted  
1834 --- = information does not need to be submitted

1835  
1836 The suitability of the container closure system used for the storage, transportation (shipping)  
1837 and use of any intermediate/in-process products (e.g. premixes, bulk FPP) should also be  
1838 discussed.

1839  
1840 A device is required to be included with the container closure system for oral liquids or solids  
1841 (e.g. solutions, emulsions, suspensions and powders/granules for such), any time the package  
1842 provides for multiple doses.

1843  
1844 In accordance with the Ph.Int. general chapter *Liquid Preparations for Oral Use*:

1845  
1846 *“Each dose from a multidose container is administered by means of a device suitable*  
1847 *for measuring the prescribed volume. The device is usually a spoon or a cup for*  
1848 *volumes of 5 ml or multiples thereof, or an oral syringe for other volumes or, for oral*  
1849 *drops, a suitable dropper.”*

1850  
1851 For a device accompanying a multidose container, the results of a study should be provided  
1852 demonstrating the reproducibility of the device (e.g. consistent delivery of the intended  
1853 volume), generally at the lowest intended dose.

1854  
1855 A sample of the device should be provided in *Module 1*.

1856  
1857 **3.2.P.2.5 Microbiological attributes (name, dosage form)**

1858  
1859 **Where appropriate, the microbiological attributes of the dosage form should be**  
1860 **discussed, including, for example, the rationale for not performing microbial limits**  
1861 **testing for non-sterile products and the selection and effectiveness of preservative**  
1862 **systems in products containing antimicrobial preservatives. For sterile products, the**  
1863 **integrity of the container closure system to prevent microbial contamination should be**  
1864 **addressed.**

1865  
1866 Where an antimicrobial preservative is included in the formulation, the amount used should  
1867 be justified by submission of results of the product formulated with different concentrations of  
1868 the preservative(s) to demonstrate the least necessary but still effective concentration. The  
1869 effectiveness of the agent should be justified and verified by appropriate studies (e.g. USP or

1870 Ph.Eur. general chapters on antimicrobial preservatives) using a batch of the FPP. If the lower  
1871 bound for the proposed acceptance criteria for the assay of the preservative is less than 90.0%,  
1872 the effectiveness of the agent should be established with a batch of the FPP containing a  
1873 concentration of the antimicrobial preservative corresponding to the lower proposed  
1874 acceptance criteria.

1875

1876 As outlined in the WHO stability guideline (WHO Technical Report Series, No. 953, Annex  
1877 2, 2009), a single primary stability batch of the FPP should be tested for effectiveness of the  
1878 antimicrobial preservative (in addition to preservative content) at the proposed shelf-life for  
1879 verification purposes, regardless of whether there is a difference between the release and  
1880 shelf-life acceptance criteria for preservative content.

1881

### 1882 **3.2.P.2.6**      *Compatibility (name, dosage form)*

1883

1884 **The compatibility of the FPP with reconstitution diluent(s) or dosage devices (e.g.**  
1885 **precipitation of API in solution, sorption on injection vessels, stability) should be**  
1886 **addressed to provide appropriate and supportive information for the labeling.**

1887

1888 Where a device is required for oral liquids or solids (e.g. solutions, emulsions, suspensions  
1889 and powders/granules for such) that are intended to be administered immediately after being  
1890 added to the device, the studies mentioned in the following paragraphs are not required.

1891

1892 Where sterile, reconstituted products are to be further diluted, compatibility should be  
1893 demonstrated with all diluents over the range of dilution proposed in the labelling. These  
1894 studies should preferably be conducted on aged samples. Where the labelling does not specify  
1895 the type of containers, compatibility (with respect to parameters such as appearance, pH,  
1896 assay, levels of individual and total degradation products, subvisible particulate matter and  
1897 extractables from the packaging components) should be demonstrated in glass, PVC and  
1898 polyolefin containers. However, if one or more containers are identified in the labelling,  
1899 compatibility of admixtures needs to be demonstrated only in the specified containers.

1900

1901 Studies should cover the duration of storage reported in the labelling (e.g. 24 hours under  
1902 controlled room temperature and 72 hours under refrigeration). Where the labelling specifies  
1903 co-administration with other FPPs, compatibility should be demonstrated with respect to the  
1904 principal FPP as well as the co-administered FPP (i.e. in addition to other aforementioned  
1905 parameters for the mixture, the assay and degradation levels of each co-administered FPP  
1906 should be reported).

1907

### 1908 **3.2.P.3**      **Manufacture (name, dosage form)**

1909

#### 1910 **3.2.P.3.1**      *Manufacturer(s) (name, dosage form)*

1911

1912 **The name, address, and responsibility of each manufacturer, including contractors, and**  
1913 **each proposed production site or facility involved in manufacturing and testing should**  
1914 **be provided.**

1915

1916 The facilities involved in the fabrication, packaging, labelling and testing should be listed. If  
1917 certain companies are responsible only for specific steps (e.g. manufacturing of an  
1918 intermediate), this should be clearly indicated. (Ref: WHO good distribution practices for  
1919 pharmaceutical products, WHO Technical Report Series, No. 957, Annex 5.)

1920

1921 The list of manufacturers/companies should specify the *actual addresses* of production or  
1922 manufacturing site(s) involved (including block(s) and unit(s)), rather than the administrative  
1923 offices.

1924  
1925 For a mixture of an API with an excipient, the blending of the API with the excipient is  
1926 considered to be the first step in the manufacture of the final product and therefore the  
1927 mixture does not fall under the definition of an API. The only exceptions are in the cases  
1928 where the API cannot exist on its own. Similarly, for a mixture of APIs, the blending of the  
1929 APIs is considered to be the first step in the manufacture of the final product. Sites for such  
1930 manufacturing steps should be included in this section.

1931  
1932 A valid manufacturing authorization for pharmaceutical production, as well as  
1933 a marketing authorization, should be submitted to demonstrate that the product is registered or  
1934 licensed in accordance with national requirements (*Module 1*, 1.2.2).

1935  
1936 For each site where the major production step(s) are carried out, when applicable, attach a  
1937 WHO-type certificate of GMP issued by the competent authority in terms of the WHO  
1938 Certification Scheme on the Quality of Pharmaceutical Products Moving in International  
1939 Commerce (*Module 1*, 1.2.2).

1940  
1941 *Justification for any differences to the product in the country or countries issuing the WHO-*  
1942 *type certificate(s)*

1943  
1944 When there are differences between the product for which this application is submitted and  
1945 that marketed in the country/countries which provided the WHO-type certificate(s), provide  
1946 data to support the applicability of the certificate(s) despite the differences. Depending on the  
1947 case, it may be necessary to provide validation data for differences in site of manufacture,  
1948 specifications, formulation, etc. Note that only minor differences are likely to be acceptable.  
1949 Differences in container labelling need not normally be justified.

1950  
1951 *Regulatory situation in other countries*

1952  
1953 The countries should be listed in which this product has been granted a marketing  
1954 authorization, this product has been withdrawn from the market and/or this application for  
1955 marketing has been rejected, deferred or withdrawn.

1956  
1957 Reference documents: WHO Technical Report Series, No. 908, Annex 4 and No. 957, Annex  
1958 5

1959  
1960 **3.2.P.3.2** *Batch formula (name, dosage form)*

1961  
1962 **A batch formula should be provided that includes a list of all components of the dosage**  
1963 **form to be used in the manufacturing process, their amounts on a per-batch basis,**  
1964 **including overages, and a reference to their quality standards.**

1965  
1966 The tables in the QOS-PD template should be used to summarize the batch formula of the  
1967 FPP *for each proposed commercial batch size* and express the quantity of each component on  
1968 a per batch basis, including a statement of the total weight or measure of the batch.

1969  
1970 All components used in the manufacturing process should be included, including those that  
1971 may not be added to every batch (e.g. acid and alkali), those that may be removed during

1972 processing (e.g. solvents) and any others (e.g. nitrogen, silicon for stoppers). If the FPP is  
1973 formulated using an active moiety, then the composition for the active ingredient should be  
1974 clearly indicated (e.g. “1 kg of active ingredient base = 1.075 kg active ingredient  
1975 hydrochloride”). All overages should be clearly indicated (e.g. “Contains 5 kg (corresponding  
1976 to 2%) overage of the API to compensate for manufacturing losses”).

1977  
1978 The components should be declared by their proper or common names, quality standards (e.g.  
1979 Ph.Int., Ph.Eur., BP, USP, House) and, if applicable, their grades (e.g. “Microcrystalline  
1980 Cellulose NF (PH 102)”) and special technical characteristics (e.g. lyophilized, micronized,  
1981 solubilised, emulsified).

1982

1983 **3.2.P.3.3** *Description of manufacturing process and process controls*  
1984 *(name, dosage form)*

1985

1986 **A flow diagram should be presented giving the steps of the process and showing where**  
1987 **materials enter the process. The critical steps and points at which process controls,**  
1988 **intermediate tests or final product controls are conducted should be identified.**

1989

1990 **A narrative description of the manufacturing process, including packaging, that**  
1991 **represents the sequence of steps undertaken and the scale of production should also be**  
1992 **provided. Novel processes or technologies and packaging operations that directly affect**  
1993 **product quality should be described with a greater level of detail. Equipment should, at**  
1994 **least, be identified by type (e.g. tumble blender, in-line homogeniser) and working**  
1995 **capacity, where relevant.**

1996

1997 **Steps in the process should have the appropriate process parameters identified, such as**  
1998 **time, temperature, or pH. Associated numeric values can be presented as an expected**  
1999 **range. Numeric ranges for critical steps should be justified in section 3.2.P.3.4. In**  
2000 **certain cases, environmental conditions (e.g. low humidity for an effervescent product)**  
2001 **should be stated.**

2002

2003 **Proposals for the reprocessing of materials should be justified. Any data to support this**  
2004 **justification should be either referenced or filed in this section (3.2.P.3.3).**

2005

2006 The information above should be summarized in the QOS-PD template and should reflect the  
2007 production of the proposed commercial batches. See Section 2. *Glossary* for definitions of  
2008 pilot-scale and production-scale batches.

2009

2010 For the manufacture of sterile products, the class (e.g. A, B, C etc.) of the areas should be  
2011 stated for each activity (e.g. compounding, filling, sealing etc), as well as the sterilization  
2012 parameters for equipment, container/closure, terminal sterilization etc.

2013

2014 Reference documents: ICH Q8, Q9, Q10

2015

2016 **3.2.P.3.4 Controls of Critical Steps and Intermediates (name, dosage form)**

2017

2018 **Critical Steps: Tests and acceptance criteria should be provided (with justification,**  
2019 **including experimental data) performed at the critical steps identified in 3.2.P.3.3 of the**  
2020 **manufacturing process, to ensure that the process is controlled.**

2021

2022 **Intermediates: Information on the quality and control of intermediates isolated during**  
2023 **the process should be provided.**

2024

2025 Examples of applicable in-process controls include:

2026

- 2027 • granulations: moisture (limits expressed as a range), blend uniformity, bulk and tapped
- 2028 densities, particle size distribution;
- 2029 • solid oral products: average weight, weight variation, hardness, thickness, friability,
- 2030 disintegration, weight gain during coating;
- 2031 • fixed-dose combinations: uniformity of content of each active prior to compression
- 2032 (tablets) or filling (e.g. capsules, sachets and suspension dosage forms);
- 2033 • semi-solids: viscosity, homogeneity, pH;
- 2034 • transdermal dosage forms: assay of API-adhesive mixture, weight per area of coated
- 2035 patch without backing;
- 2036 • metered dose inhalers: fill weight/volume, leak testing, valve delivery;
- 2037 • dry powder inhalers: assay of API-excipient blend, moisture, weight variation of
- 2038 individually contained doses such as capsules or blisters;
- 2039 • liquids: pH, specific gravity, clarity of solutions; and
- 2040 • parenterals: appearance, clarity, fill volume/weight, pH, filter integrity tests,
- 2041 particulate matter, leak testing of ampoules.

2042

2043 Reference documents: ICH Q2, Q6A, Q8, Q9, Q10, WHO Technical Report Series, No. 929,  
2044 Annex 5

2045

### 2046 **3.2.P.3.5 Process validation and/or evaluation (name, dosage form)**

2047

2048 **Description, documentation, and results of the validation and/or evaluation studies**  
2049 **should be provided for critical steps or critical assays used in the manufacturing process**  
2050 **(e.g. validation of the sterilisation process or aseptic processing or filling). Viral safety**  
2051 **evaluation should be provided in 3.2A.2, if necessary.**

2052

2053 For products that meet the criteria of an *established multisource product*, a product quality  
2054 review as outlined in Appendix 2 may be submitted in lieu of the information below.

2055

2056 The following information should be provided for all other products:

2057

- 2058 a) a copy of the *process validation protocol*, specific to this FPP, that identifies the  
2059 critical equipment and process parameters that can affect the quality of the FPP and  
2060 defines testing parameters, sampling plans, analytical procedures and acceptance  
2061 criteria;
- 2062
- 2063 b) a *commitment* that three consecutive, production-scale batches of this FPP will be  
2064 subjected to *prospective validation* in accordance with the above protocol; The  
2065 applicant should submit a written commitment that information from these studies will  
2066 be available for verification after prequalification by the WHO inspection team; and
- 2067
- 2068 c) if the process validation studies have already been conducted (e.g. for sterile  
2069 products), a copy of the *process validation report* should be provided in the PD in lieu  
2070 of (a) and (b) above.

2071

2072 One of the most practical forms of process validation, mainly for non-sterile products, is the  
2073 final testing of the product to an extent greater than that required in routine quality control. It  
2074 may involve extensive sampling, far beyond that called for in routine quality control and  
2075 testing to normal quality control specifications and often for certain parameters only. Thus,  
2076 for instance, several hundred tablets per batch may be weighed to determine unit dose  
2077 uniformity. The results are then treated statistically to verify the "normality" of the  
2078 distribution and to determine the standard deviation from the average weight. Confidence  
2079 limits for individual results and for batch homogeneity are also estimated. Strong assurance is  
2080 provided that samples taken at random will meet regulatory requirements if the confidence  
2081 limits are well within compendial specifications.

2082 Similarly, extensive sampling and testing may be performed with regard to any quality  
2083 requirements. In addition, intermediate stages may be validated in the same way, e.g. dozens  
2084 of samples may be assayed individually to validate mixing or granulation stages of low-dose  
2085 tablet production by using the content uniformity test. Products (intermediate or final) may  
2086 occasionally be tested for non-routine characteristics. Thus, subvisual particulate matter in  
2087 parenteral preparations may be determined by means of electronic devices, or tablets/capsules  
2088 tested for dissolution profile if such tests are not performed on every batch.  
2089

2090 Where ranges of batch sizes are proposed, it should be shown that variations in batch size  
2091 would not adversely alter the characteristics of the finished product. It is envisaged that those  
2092 parameters listed in the following validation scheme will need to be re-validated once further  
2093 scale-up is proposed after prequalification.  
2094

2095 The process validation protocol should include inter alia the following:

- 2096
- 2097 – a reference to the current master production document;
  - 2098 – a discussion of the critical equipment;
  - 2099 – the process parameters that can affect the quality of the FPP (critical process  
2100 parameters (CPPs)) including challenge experiments and failure mode  
2101 operation;
  - 2102 – details of the sampling: sampling points, stages of sampling, methods of  
2103 sampling and the sampling plans (including schematics of blender/storage bins  
2104 for testing of the final blend);
  - 2105 – the testing parameters/acceptance criteria including in-process and release  
2106 specifications;
  - 2107 – the analytical procedures or a reference to appropriate section(s) of the dossier;
  - 2108 – the methods for recording/evaluating results; and
  - 2109 – the proposed timeframe for completion of the protocol.  
2110

2111 The manufacture of sterile FPPs needs a well-controlled manufacturing area (e.g. a strictly  
2112 controlled environment, highly reliable procedures and appropriate in-process controls). A  
2113 detailed description of these conditions, procedures and controls should be provided, together  
2114 with actual copies of the following standard operating procedures:  
2115

- 2116 a) washing, treatment, sterilizing and depyrogenating of containers, closures and  
2117 equipment;
- 2118 b) filtration of solutions;
- 2119 c) lyophilization process;
- 2120 d) leaker test of filled and sealed ampoules;
- 2121 e) final inspection of the product; and

2122 f) sterilization cycle.

2123

2124 The sterilization process used to destroy or remove microorganisms is probably the single  
2125 most important process in the manufacture of parenteral FPPs. The process can make use of  
2126 moist heat (e.g. steam), dry heat, filtration, gaseous sterilization (e.g. ethylene oxide), or  
2127 radiation. It should be noted that terminal steam sterilization, when practical, is considered to  
2128 be the method of choice to ensure sterility of the final FPP. Therefore, scientific justification  
2129 for selecting any other method of sterilization should be provided.

2130

2131 The sterilization process should be described in detail and evidence should be provided to  
2132 confirm that it will produce a sterile product with a high degree of reliability and that the  
2133 physical and chemical properties as well as the safety of the FPP will not be affected. Details  
2134 such as Fo range, temperature range and peak dwell time for an FPP and the container closure  
2135 should be provided. Although standard autoclaving cycles of 121°C for 15 minutes or more  
2136 would not need a detailed rationale, such justifications should be provided for reduced  
2137 temperature cycles or elevated temperature cycles with shortened exposure times. If ethylene  
2138 oxide is used, studies and acceptance criteria should control the levels of residual ethylene  
2139 oxide and related compounds.

2140

2141 Filters used should be validated with respect to pore size, compatibility with the product,  
2142 absence of extractables and lack of adsorption of the API or any of the components.

2143

2144 For the validation of aseptic filling of parenteral products that cannot be terminally sterilized,  
2145 simulation process trials should be conducted. This involves filling ampoules with culture  
2146 media under normal conditions, followed by incubation and control of microbial growth. A  
2147 level of contamination of less than 0.1% is considered to be acceptable.

2148

2149 Reference documents: ICH Q8, Q9, Q10, WHO Technical Report Series, Nos. 902 and 908

2150

### 2151 **3.2.P.4 Control of excipients (name, dosage form)**

2152

#### 2153 **3.2.P.4.1 Specifications (name, dosage form)**

2154

2155 **The specifications for excipients should be provided.**

2156

2157 The specifications from the applicant or the FPP manufacturer should be provided for all  
2158 excipients, including those that may not be added to every batch (e.g. acid and alkali), those  
2159 that do not appear in the final FPP (e.g. solvents) and any others used in the manufacturing  
2160 process (e.g. nitrogen, silicon for stoppers).

2161

2162 If the standard claimed for an excipient is an officially recognized compendial standard, it is  
2163 sufficient to state that the excipient is tested according to the requirements of that standard,  
2164 rather than reproducing the specifications found in the officially recognized compendial  
2165 monograph.

2166

2167 If the standard claimed for an excipient is a non-compendial standard (e.g. House standard) or  
2168 includes tests that are supplementary to those appearing in the officially recognized  
2169 compendial monograph, a copy of the specification for the excipient should be provided.

2170

2171 For products submitted to the Prequalification Programme, non-compendial excipients should  
2172 not be used.

2173

2174 For excipients of natural origin, microbial limit testing should be included in the  
2175 specifications. Skip testing is acceptable if justified (submission of acceptable results of five  
2176 production batches).

2177

2178 For oils of plant origin (e.g. soy bean oil, peanut oil) the absence of aflatoxins or biocides  
2179 should be demonstrated.

2180

2181 The colours permitted for use are limited to those listed in the “Japanese pharmaceutical  
2182 excipients”, the EU “List of permitted food colours”, and the FDA “Inactive ingredient  
2183 guide”. For proprietary mixtures, the supplier’s product sheet with the qualitative formulation  
2184 should be submitted, in addition to the FPP manufacturer’s specifications for the product  
2185 including identification testing.

2186

2187 For flavours the qualitative composition should be submitted, as well as a declaration that the  
2188 excipients comply with foodstuff regulations (e.g. USA or EU).

2189

2190 Information that is considered confidential may be submitted directly to the WHO  
2191 Prequalification Programme by the supplier with reference to the specific related product.

2192

2193 Other certifications of at-risk components may be required on a case-by-case basis.

2194

2195 If additional purification is undertaken on commercially available excipients details of the  
2196 process of purification and modified specifications should be submitted.

2197

2198 Reference documents: ICH Q6A

2199

#### 2200 **3.2.P.4.2** *Analytical procedures (name, dosage form)*

2201

2202 **The analytical procedures used for testing the excipients should be provided, where**  
2203 **appropriate.**

2204

2205 Copies of analytical procedures from officially recognized compendial monographs do not  
2206 need to be submitted.

2207

2208 Reference documents: ICH Q2

2209

#### 2210 **3.2.P.4.3** *Validation of analytical procedures (name, dosage form)*

2211

2212 **Analytical validation information, including experimental data, for the analytical**  
2213 **procedures used for testing the excipients should be provided, where appropriate.**

2214

2215 Copies of analytical validation information are normally not submitted for the testing of  
2216 excipients.

2217

2218 Reference documents: ICH Q2

2219

#### 2220 **3.2.P.4.4** *Justification of specifications (name, dosage form)*

2221

2222 **Justification for the proposed excipient specifications should be provided, where**  
2223 **appropriate.**

2224  
2225 A discussion of the tests that are supplementary to those appearing in the officially recognized  
2226 compendial monograph should be provided.

2227  
2228 **3.2.P.4.5 Excipients of human or animal origin (name, dosage form)**  
2229

2230 **For excipients of human or animal origin, information should be provided regarding**  
2231 **adventitious agents (e.g. sources, specifications, description of the testing performed,**  
2232 **viral safety data) (details in 3.2.A.2).**  
2233

2234 The following excipients should be addressed in this section: gelatin, phosphates, stearic acid,  
2235 magnesium stearate and other stearates. If from plant origin a declaration to this effect will  
2236 suffice.

2237 For these excipients from animal origin, a letter of attestation should be provided confirming  
2238 that the excipients used to manufacture the FPP are *without* risk of transmitting agents of  
2239 animal spongiform encephalopathies.

2240  
2241 Materials of animal origin should be avoided whenever possible.

2242  
2243 When available, a CEP demonstrating TSE-compliance should be provided. A complete copy  
2244 of the CEP (including any annexes) should be provided in Module 1.

2245  
2246 Reference documents: ICH Q5A, Q5D, Q6B, WHO Technical Report Series, No. 908, Annex  
2247 1

2248  
2249 **3.2.P.4.6 Novel excipients (name, dosage form)**  
2250

2251 **For excipient(s) used for the first time in an FPP or by a new route of administration,**  
2252 **full details of manufacture, characterisation, and controls, with cross references to**  
2253 **supporting safety data (nonclinical and/or clinical) should be provided according to the**  
2254 **API and/or FPP format (details in 3.2.A.3).**  
2255

2256 Novel excipients are not accepted in the Prequalification Programme.

2257  
2258 **3.2.P.5 Control of FPP (name, dosage form)**  
2259

2260 **3.2.P.5.1 Specification(s) (name, dosage form)**  
2261

2262 **The specification(s) for the FPP should be provided.**  
2263

2264 As defined in ICH's Q6A guideline, a specification is:

2265  
2266 *“a list of tests, references to analytical procedures and appropriate acceptance*  
2267 *criteria, which are numerical limits, ranges, or other criteria for the tests described. It*  
2268 *establishes the set of criteria to which an API or FPP should conform to be*  
2269 *considered acceptable for its intended use. “Conformance to specifications” means*  
2270 *that the API and / or FPP, when tested according to the listed analytical procedures,*  
2271 *will meet the listed acceptance criteria. Specifications are critical quality standards*  
2272 *that are proposed and justified by the manufacturer and approved by regulatory*  
2273 *authorities.”*

2274

2275 A copy of the FPP specification(s) from the applicant (as well as the company responsible for  
2276 the batch release of the FPP, if different from the applicant), dated and signed by authorized  
2277 personnel (i.e. the person in charge of the quality control or quality assurance department)  
2278 should be provided in the PD. Two separate sets of specifications may be set out: after  
2279 packaging of the FPP (release) and at the end of shelf-life.

2280

2281 The specifications should be summarized according to the tables in the QOS-PD template  
2282 including the tests, acceptance criteria and analytical procedures (including types, sources and  
2283 versions for the methods):

2284

- 2285 • the *standard* declared by the applicant could be an officially recognized compendial  
2286 standard (e.g. Ph.Int., BP, USP) or a House (manufacturer's) standard;
- 2287 • the *specification reference number and version* (e.g. *revision number and/or date*)  
2288 should be provided for version control purposes;
- 2289 • for the analytical procedures, the *type* should indicate the kind of analytical procedure  
2290 used (e.g. visual, IR, UV, HPLC), the *source* refers to the origin of the analytical  
2291 procedure (e.g. Ph.Int., Ph.Eur., BP, USP, in-house) and the *version* (e.g. *code*  
2292 *number/version/date*) should be provided for version control purposes.

2293

2294 ICH's Q6A guideline outlines recommendations for a number of *universal* and *specific tests*  
2295 and criteria for FPPs. Specifications should include, at minimum, tests for appearance,  
2296 identification, assay, purity, pharmaceutical tests (e.g. dissolution), physical tests (e.g. loss on  
2297 drying, hardness, friability, particle size, apparent density), uniformity of dosage units,  
2298 identification of colouring materials, identification and assay of antimicrobial or chemical  
2299 preservatives (e.g. antioxidants) and microbial limit tests.

2300

2301 The following information provides guidance for specific tests that are not addressed by  
2302 ICH's Q6A guideline:

2303

- 2304 • fixed-dose combination FPPs (FDC-FPPs):
  - 2305 ○ analytical methods that can distinguish each API in the presence of the other  
2306 API(s) should be developed and validated,
  - 2307 ○ acceptance criteria for degradation products should be established with  
2308 reference to the API they are derived from. If an impurity results from a  
2309 chemical reaction between two or more APIs, its acceptance limits should be  
2310 calculated with reference to the worst case (the API with the smaller area under  
2311 the curve). Alternatively the content of such impurities could be calculated in  
2312 relation to their reference standards,
  - 2313 ○ when any one API is present at less than 25 mg or less than 25% of the weight  
2314 of the dosage unit, a test and limit for content uniformity is required for each  
2315 API in the FPP,
  - 2316 ○ when all APIs are present at greater than 25 mg and greater than 25% of the  
2317 weight of the dosage unit, a test and limit for weight variation may be  
2318 established for each API in the FPP, in lieu of content uniformity testing;
- 2319 • modified-release products: a meaningful API release method;
- 2320 • inhalation and nasal products: consistency of delivered dose (throughout the use of the  
2321 product), particle or droplet size distribution profiles (comparable to the product used  
2322 in in vivo studies, where applicable) and if applicable for the dosage form, moisture  
2323 content, leak rate, microbial limits, preservative assay, sterility and weight loss;

- 2324       • suppositories: uniformity of dosage units, melting point; and  
2325       • transdermal dosage forms: peel or shear force, mean weight per unit area, dissolution.  
2326

2327 Unless there is appropriate justification, the acceptable limit for the API content of the FPP in  
2328 the release specifications is  $\pm 5\%$  of the label claim (i.e. 95.0-105.0%).  
2329

2330 Skip testing is acceptable for parameters such as identification of colouring materials and  
2331 microbial limits, when justified by the submission of acceptable supportive results for five  
2332 production batches. When skip testing justification has been accepted, the specifications  
2333 should include a footnote, stating at minimum the following skip testing requirements: NLT  
2334 every tenth batch and at least one batch annually is tested. In addition, for stability-indicating  
2335 parameters such as microbial limits, testing will be performed at release and shelf-life during  
2336 stability studies.  
2337

2338 Any differences between release and shelf-life tests and acceptance criteria should be clearly  
2339 indicated and justified. Note that such differences for parameters such as dissolution are  
2340 normally not accepted.  
2341

2342 Reference documents: ICH Q3B, Q3C, Q6A  
2343

#### 2344 **3.2.P.5.2       Analytical procedures (name, dosage form)**

2345

2346 **The analytical procedures used for testing the FPP should be provided.**  
2347

2348 Copies of the in-house analytical procedures used during pharmaceutical development (if used  
2349 to generate testing results provided in the PD) as well as those proposed for routine testing  
2350 should be provided. Unless modified, it is not necessary to provide copies of officially  
2351 recognized compendial analytical procedures.  
2352

2353 Tables for summarizing a number of the different analytical procedures and validation  
2354 information (e.g. HPLC assay/impurity methods) can be found in the 2.3.R Regional  
2355 information section of the QOS-PD (i.e. 2.3.R.2). These tables should be used to summarize  
2356 the analytical procedures used for determination of the assay, related substances and  
2357 dissolution of the FPP.  
2358

2359 Refer to section 3.2.S.4.2 of this guideline for additional guidance on analytical procedures.  
2360

2361 Reference documents: ICH Q2  
2362

#### 2363 **3.2.P.5.3       Validation of analytical procedures (name, dosage form)**

2364

2365 **Analytical validation information, including experimental data, for the analytical**  
2366 **procedures used for testing the FPP, should be provided.**  
2367

2368 Copies of the validation reports for the in-house analytical procedures used during  
2369 pharmaceutical development (if used to support testing results provided in the PD) as well as  
2370 those proposed for routine testing should be provided.  
2371

2372 Tables for summarizing a number of the different analytical procedures and validation  
2373 information (e.g. HPLC assay/impurity methods, GC methods) can be found in the 2.3.R  
2374 Regional information section of the QOS-PD (i.e. 2.3.R.2). These tables should be used to

2375 summarize the validation information of the analytical procedures used for determination of  
2376 the assay, related substances and dissolution of the FPP.

2377

2378 As recognized by regulatory authorities and pharmacopoeias themselves, verification of  
2379 compendial methods can be necessary. The compendial methods, as published, are typically  
2380 validated based on an API or an FPP originating from a specific manufacturer. Different  
2381 sources of the same API or FPP can contain impurities and/or degradation products or  
2382 excipients that were not considered during the development of the monograph. Therefore the  
2383 monograph and compendial method(s) should be demonstrated suitable for the control of the  
2384 proposed FPP.

2385

2386 For officially recognized compendial FPP *assay* methods, verification should include a  
2387 demonstration of specificity, accuracy and repeatability (method precision). If an officially  
2388 recognized compendial method is used to control related substances that are not specified in  
2389 the monograph, full validation of the method is expected with respect to those related  
2390 substances.

2391

2392 If an officially recognized compendial standard is claimed and an in-house method is used in  
2393 lieu of the compendial method (e.g. for assay or for related compounds), equivalency of the  
2394 in-house and compendial methods should be demonstrated. This could be accomplished by  
2395 performing duplicate analyses of one sample by both methods and providing the results from  
2396 the study. For related compound methods, the sample analyzed should be the FPP spiked  
2397 with related compounds at concentrations equivalent to their specification limits.

2398

2399 Reference documents: ICH Q2

2400

#### 2401 **3.2.P.5.4      *Batch analyses (name, dosage form)***

2402

2403 **A description of batches and results of batch analyses should be provided.**

2404

2405 Information should include strength and batch number, batch size, date and site of production  
2406 and use (e.g. used in comparative bioavailability or biowaiver studies, stability, pilot, scale-up  
2407 and, if available, production-scale batches) on relevant FPP batches used to establish the  
2408 specification(s) and evaluate consistency in manufacturing.

2409

2410 Analytical results tested by the company responsible for the batch release of the FPP  
2411 (generally, the applicant or the FPP manufacturer, if different from the applicant) should be  
2412 provided for not less than two batches of at least pilot scale, or in the case of an  
2413 uncomplicated<sup>2</sup> FPP (e.g. immediate-release solid FPPs (with noted exceptions), non-sterile  
2414 solutions), not less than one batch of at least pilot scale and a second batch which may be  
2415 smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules) of each  
2416 proposed strength of the FPP. These batches should be manufactured by a procedure fully  
2417 representative of and simulating that to be applied to a full production-scale batch.

2418

---

<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. Due to the rolling nature of the products listed in the invitations for EOI, the listing of individual "complicated" FPPs is not meaningful and applicants should contact the assessment manager in case of doubt.

2419 The testing results should include the batch(es) used in the comparative bioavailability or  
2420 biowaiver studies. Copies of the certificates of analysis for these batches should be provided  
2421 in the PD and the company responsible for generating the testing results should be identified.  
2422

2423 The discussion of results should focus on observations noted for the various tests, rather than  
2424 reporting comments such as “all tests meet specifications”. This should include ranges of  
2425 analytical results, where relevant. For quantitative tests (e.g. individual and total impurity  
2426 tests and assay tests), it should be ensured that actual *numerical results* are provided rather  
2427 than vague statements such as “within limits” or “conforms” (e.g. “levels of degradation  
2428 product A ranged from 0.2 to 0.4%”). Dissolution results should be expressed at minimum as  
2429 both the average and range of individual results. Recommendations for conducting and  
2430 assessing comparative dissolution profiles can be found in Appendix 1.  
2431

2432 A discussion and justification should be provided for any incomplete analyses (e.g. results not  
2433 tested according to the proposed specification).  
2434

2435 Reference documents: ICH Q3B, Q3C, Q6A  
2436

### 2437 **3.2.P.5.5**      *Characterization of impurities (name, dosage form)* 2438

2439 **Information on the characterization of impurities should be provided, if not previously**  
2440 **provided in “3.2.S.3.2 Impurities”.**  
2441

2442 A discussion should be provided of all impurities that are potential degradation products  
2443 (including those among the impurities identified in 3.2.S.3.2 as well as potential degradation  
2444 products resulting from interaction of the API with other APIs (FDCs), excipients or the  
2445 container closure system) and FPP process-related impurities (e.g. residual solvents in the  
2446 manufacturing process for the FPP).  
2447

2448 Reference documents: ICH Q3B, Q3C, Q6A  
2449

### 2450 **3.2.P.5.6**      *Justification of specification(s) (name, dosage form)* 2451

2452 **Justification for the proposed FPP specification(s) should be provided.**  
2453

2454 A discussion should be provided on the omission or inclusion of certain tests, evolution of  
2455 tests, analytical procedures and acceptance criteria, differences from the officially recognized  
2456 compendial standard(s), etc. If the officially recognized compendial methods have been  
2457 modified or replaced, a discussion should be included.  
2458

2459 The justification for certain tests, analytical procedures and acceptance criteria (e.g.  
2460 degradation products, dissolution method development) may have been discussed in other  
2461 sections of the PD and does not need to be repeated here, although a cross-reference to their  
2462 location should be provided.  
2463

2464 ICH Q6A should be consulted for the development of specifications for FPPs.  
2465

2466 **3.2.P.6 Reference standards or materials (name, dosage form)**

2467

2468 **Information on the reference standards or reference materials used for testing of the**  
2469 **FPP should be provided, if not previously provided in “3.2.S.5 Reference standards or**  
2470 **materials”.**

2471

2472 See Section 3.2.S.5 for information that should be provided on reference standards or  
2473 materials. Information should be provided on reference materials of FPP degradation  
2474 products, where not included in 3.2.S.5.

2475

2476 Reference documents: ICH Q6A, WHO Technical Report Series, No. 943, Annex 3

2477

2478 **3.2.P.7 Container closure system (name, dosage form)**

2479

2480 **A description of the container closure systems should be provided, including the identity**  
2481 **of materials of construction of each primary packaging component and its specification.**  
2482 **The specifications should include description and identification (and critical dimensions,**  
2483 **with drawings where appropriate). Non-compendial methods (with validation) should be**  
2484 **included, where appropriate.**

2485

2486 **For non-functional secondary packaging components (e.g. those that neither provide**  
2487 **additional protection nor serve to deliver the product), only a brief description should be**  
2488 **provided. For functional secondary packaging components, additional information**  
2489 **should be provided.**

2490

2491 **Suitability information should be located in 3.2.P.2.**

2492

2493 The WHO *Guidelines on packaging for pharmaceutical products* (WHO Technical Report  
2494 Series, No. 902, Annex 9, 2002) and the officially recognized pharmacopoeias should be  
2495 consulted for recommendations on the packaging information for FPPs.

2496

2497 Descriptions, materials of construction and specifications (of the company responsible for  
2498 packaging the FPP, generally the FPP manufacturer) should be provided for the packaging  
2499 components that are:

2500

- 2501 • in direct contact with the dosage form (e.g. container, closure, liner, desiccant, filler);
- 2502 • used for drug delivery (including the device(s) for multi-dose solutions, emulsions,  
2503 suspensions and powders/granules for such);
- 2504 • used as a protective barrier to help ensure stability or sterility; and
- 2505 • necessary to ensure FPP quality during storage and shipping.

2506

2507 Primary packaging components are those that are in direct contact with the API or FPP.

2508

2509 The specifications for the primary packaging components should include a specific test for  
2510 identification (e.g. IR). Specifications for film and foil materials should include limits for  
2511 thickness or area weight.

2512

2513 Information to establish the suitability (e.g. qualification) of the container closure system  
2514 should be discussed in Section 3.2.P.2. Comparative studies may be warranted for certain

2515 changes in packaging components (e.g. comparative delivery study (droplet size) for a change  
2516 in manufacturer of dropper tips).

2517

### 2518 **3.2.P.8 Stability (name, dosage form)**

2519

#### 2520 **3.2.P.8.1 Stability summary and conclusions (name, dosage form)**

2521

2522 **The types of studies conducted, protocols used, and the results of the studies should be**  
2523 **summarised. The summary should include, for example, conclusions with respect to**  
2524 **storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-**  
2525 **life.**

2526

2527 The WHO stability guideline *Stability testing of active pharmaceutical ingredients and*  
2528 *finished pharmaceutical products* (WHO Technical Report Series, No. 953, Annex 2, 2009)  
2529 should be consulted for recommendations on the core stability data package required for the  
2530 prequalification of APIs and FPPs.

2531

2532 As outlined in the WHO stability guideline, the purpose of stability testing is to provide  
2533 evidence of how the quality of an API or FPP varies with time under the influence of a variety  
2534 of environmental factors such as temperature, humidity and light. The stability programme  
2535 also includes the study of product-related factors that influence its quality, for example,  
2536 interaction of API with excipients, container closure systems and packaging materials.

2537

#### 2538 *Stress testing*

2539

2540 As outlined in the WHO stability guideline, photostability testing should be conducted on at  
2541 least one primary batch of the FPP if appropriate. If “protect from light” is stated in one of  
2542 the officially recognized pharmacopoeia for the API or FPP, it is sufficient to state “protect  
2543 from light” on labelling, in lieu of photostability studies, when the container closure system is  
2544 shown to be light protective. Additional stress testing of specific types of dosage forms may  
2545 be appropriate (e.g. cyclic studies for semi-solid products, freeze-thaw studies for liquid  
2546 products).

2547

#### 2548 *Accelerated, intermediate (if necessary) and long-term testing*

2549

2550 Stability data must demonstrate stability of the medicinal product throughout its intended

2551 shelf-life under the climatic conditions prevalent in the target countries. Merely applying the

2552 same requirements applicable to other markets could potentially lead to substandard products,  
2553 e.g. stability studies conducted for countries in Climatic Zone I/II when the products are  
2554 supplied in Climatic Zones III and IV countries. Refer to WHO Technical Report Series, No.  
2555 953, Annex 2, Appendix 1 for information on climatic zones. Effective as of September 2011,  
2556 the required long-term storage conditions for the Prequalification Programme are  
2557 30°C±2°C/75%±5%RH, and after this date the long-term data submitted in the PD (see table  
2558 below) should be at these conditions. The use of alternative long-term conditions will need to  
2559 be justified and should be supported with appropriate evidence.

2560

2561 Other storage conditions are outlined in the WHO stability guideline for FPPs packaged in  
2562 impermeable and semi-permeable containers and those intended for storage in a refrigerator  
2563 and in a freezer. FPPs intended for storage below -20°C should be treated on a case-by-case  
2564 basis.

2565

2566 The minimum data required at the time of submitting the dossier (in the general case):

2567

2568

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

2569 \*Where long-term conditions are 30°C±2°C/75%±5%RH, there is no intermediate condition.

2570

2571 Refer to WHO Technical Report Series, No. 953, Annex 2 for further information regarding  
2572 the storage conditions. Reference should also be made to the Prequalification Programme  
2573 website for any exceptions to the stated requirements.

2574

2575 To establish the shelf-life, data should be provided on not less than two batches of at least  
2576 pilot scale, or in the case of an uncomplicated FPP (e.g. immediate-release solid FPPs (with  
2577 noted exceptions), non-sterile solutions), not less than one batch of at least pilot scale and a  
2578 second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets  
2579 or capsules) of each proposed strength of the FPP. These batches should be manufactured by  
2580 a procedure fully representative of and simulating that to be applied to a full production-scale  
2581 batch.

2582

2583 The stability testing programme should be summarized and the results of stability testing  
2584 should be reported in the dossier and summarized in the tables in the QOS-PD. Bracketing  
2585 and matrixing of proportional strengths can be applied, if scientifically justified.

2586

2587 For sterile products sterility should be reported at the beginning and end of shelf-life. For  
2588 parenteral products, subvisible particulate matter should be reported frequently, but not  
2589 necessarily at every test interval. Bacterial endotoxins need only be reported at the initial test  
2590 interval. Weight loss from plastic containers should be reported over the shelf-life. In-use  
2591 periods for parenteral and ophthalmic products should be justified with experimental data.

2592

2593 The information on the stability studies should include details such as

2594

- 2595 • storage conditions;
- 2596 • strength;
- 2597 • batch number, including the API batch number(s) and manufacturer(s);
- 2598 • batch size;
- 2599 • container closure system including orientation (e.g. erect, inverted, on-side) where  
2600 applicable; and
- 2601 • completed (and proposed) test intervals.

2602

2603 The discussion of results should focus on observations noted for the various tests, rather than  
2604 reporting comments such as “all tests meet specifications”. This should include ranges of  
2605 analytical results and any trends that were observed. For quantitative tests (e.g. individual and

2606 total degradation product tests and assay tests), it should be ensured that actual numerical  
2607 results are provided rather than vague statements such as “within limits” or “conforms”.  
2608 Dissolution results should be expressed at minimum as both the average and range of  
2609 individual results.

2610  
2611 Applicants should consult ICH’s Q1E guideline for details on the evaluation and extrapolation  
2612 of results from stability data (e.g. if significant change was not observed within 6 months at  
2613 accelerated condition and the data show little or no variability, the proposed shelf-life could  
2614 be up to two times the period covered by the long-term data, but should not exceed the long-  
2615 term data by 12 months).

2616  
2617 *Proposed storage statement and shelf-life*

2618  
2619 The proposed storage statement and shelf-life (and in-use storage conditions and in-use  
2620 period, if applicable) for the FPP should be provided.

2621  
2622 The recommended labelling statements for use, based on the stability studies, are provided in  
2623 the WHO stability guideline.

2624  
2625 Reference documents: WHO Technical Report Series, No. 953, Annex 2, ICH Q1A, Q1B,  
2626 Q1C, Q1D, Q1E, Q3B, Q6A

2627  
2628 **3.2.P.8.2** *Post-approval stability protocol and stability commitment*  
2629 *(name, dosage form)*

2630  
2631 **The post-approval stability protocol and stability commitment should be provided.**

2632  
2633 *Primary stability study commitment*

2634  
2635 When available long-term stability data on primary batches do not cover the proposed shelf-  
2636 life granted at the time of assessment of the PD, a commitment should be made to continue  
2637 the stability studies in order to firmly establish the shelf-life. A written commitment (signed  
2638 and dated) to continue long-term testing over the shelf-life period should be included in the  
2639 dossier.

2640  
2641 *Commitment stability studies*

2642  
2643 The long-term stability studies for the *Commitment batches* should be conducted through the  
2644 proposed shelf-life on at least three production batches of each strength in each container  
2645 closure system. Where stability data was not provided for three production batches of each  
2646 strength, a written commitment (signed and dated) should be included in the dossier.

2647  
2648 *Ongoing stability studies*

2649  
2650 As described in the WHO stability guideline, an *ongoing stability programme* is established to  
2651 monitor the product over its shelf-life and to determine that the product remains and can be  
2652 expected to remain within specifications under the storage conditions on the label. Unless  
2653 otherwise justified, at least one batch per year of product manufactured in every strength and  
2654 every container closure system, if relevant, should be included in the stability programme  
2655 (unless none is produced during that year). Bracketing and matrixing may be applicable. A  
2656 written commitment (signed and dated) to this effect should be included in the dossier.

2657

2658 Any differences in the stability protocols used for the primary batches and those proposed for  
2659 the *commitment batches* or *ongoing batches* should be scientifically justified.

2660

2661 Reference documents: ICH Q1A

2662

### 2663 **3.2.P.8.3**      *Stability data (name, dosage form)*

2664

2665 **Results of the stability studies should be presented in an appropriate format (e.g.**  
2666 **tabular, graphical, narrative). Information on the analytical procedures used to**  
2667 **generate the data and validation of these procedures should be included.**

2668

2669 **Information on characterization of impurities is located in 3.2.P.5.5.**

2670

2671 The actual stability results/reports used to support the proposed shelf-life should be provided  
2672 in the PD. For quantitative tests (e.g. individual and total degradation product tests and assay  
2673 tests), it should be ensured that actual numerical results are provided rather than vague  
2674 statements such as “within limits” or “conforms”. Dissolution results should be expressed at  
2675 minimum as both the average and range of individual results.

2676

2677 Reference documents: ICH Q1A, Q1B, Q1C, Q1D, Q1E, Q2

2678

## 2679 **3.2.A Appendices**

2680

### 2681 **3.2.A.1**      **Facilities and equipment**

2682

2683 Not applicable (i.e. not a biotech product).

2684

### 2685 **3.2.A.2**      **Adventitious agents safety evaluation**

2686

### 2687 **3.2.A.3**      **Novel excipients**

2688

2689 Novel excipients are not accepted in the Prequalification Programme.

2690

## 2691 **3.2.R Regional information**

2692

### 2693 **3.2.R.1**      **Production documentation**

2694

#### 2695 **3.2.R.1.1**      *Executed production documents*

2696

2697 A minimum of two batches of at least pilot scale, or in the case of an uncomplicated FPP (e.g.  
2698 immediate-release solid FPPs (with noted exceptions), non-sterile solutions), not less than one  
2699 batch of at least pilot scale (the batch used in comparative bioavailability or biowaiver  
2700 studies) and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or  
2701 50 000 tablets or capsules), should be manufactured for each strength. These batches should  
2702 be manufactured by a procedure fully representative of and simulating that to be applied to a  
2703 full production-scale batch.

2704

2705 For solid oral dosage forms, *pilot scale* is generally, at a minimum, one-tenth that of full  
2706 production scale or 100 000 tablets or capsules, whichever is the larger.

2707

2708 Copies of the executed production documents should be provided for the batches used in the  
2709 comparative bioavailability or biowaiver studies. Any notations made by operators on the  
2710 executed production documents should be clearly legible.

2711  
2712 If not included in the executed batch records through sufficient in-process testing, data should  
2713 be provided for the batch used in comparative bioavailability or biowaiver studies that  
2714 demonstrates the uniformity of this batch. The data to establish the uniformity of the biobatch  
2715 should involve testing to an extent greater than that required in routine quality control.

2716  
2717 English translations of executed records should be provided, where relevant.

2718  
2719 **3.2.R.1.2 Master production documents**

2720  
2721 Copies of the FPP master production documents should be provided for each proposed  
2722 strength, commercial batch size and manufacturing site.

2723  
2724 The details in the master production documents should include, but not be limited to, the  
2725 following:

- 2726  
2727 a) master formula;
- 2728  
2729 b) dispensing, processing and packaging sections with relevant material and operational  
2730 details;
- 2731  
2732 c) relevant calculations (e.g. if the amount of API is adjusted based on the assay results  
2733 or on the anhydrous basis);
- 2734  
2735 d) identification of all equipment by, at minimum, type and working capacity (including  
2736 make, model and equipment number, where possible);
- 2737  
2738 e) process parameters (e.g. mixing time, mixing speed, milling screen size, processing  
2739 temperature range, granulation end-point, tablet machine speed (expressed as target  
2740 and range));
- 2741  
2742 f) list of in-process tests (e.g. appearance, pH, assay, blend uniformity, viscosity, particle  
2743 size distribution, LOD, weight variation, hardness, disintegration time, weight gain  
2744 during coating, leaker test, minimum fill, clarity, filter integrity checks) and  
2745 specifications;
- 2746  
2747 g) sampling plan with regard to the:
- 2748  
2749 i. steps where sampling should be done (e.g. drying, lubrication, compression),  
2750 ii. number of samples that should be tested (e.g. for blend uniformity testing of  
2751 low dose FPPs, blend drawn using a sampling thief from x positions in the  
2752 blender),  
2753 iii. frequency of testing (e.g. weight variation every x minutes during compression  
2754 or capsule filling);
- 2755  
2756 h) precautions necessary to ensure product quality (e.g. temperature and humidity  
2757 control, maximum holding times);
- 2758

- 2759 i) for sterile products, reference to SOPs in appropriate sections and a list of all relevant  
2760 SOPs at the end of the document;  
2761  
2762 j) theoretical and actual yield;  
2763  
2764 k) compliance with the GMP requirements.  
2765

2766 Reference documents: WHO Technical Report Series, Nos. 902 and No. 908  
2767

### 2768 **3.2.R.2 Analytical procedures and validation information** 2769

2770 The tables presented in section 2.3.R.2 in the QOS-PD template should be used to summarize  
2771 the analytical procedures and validation information from sections 3.2.S.4.2, 3.2.S.4.3,  
2772 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.  
2773

#### 2774 4.3 Literature references 2775

2776 References to the scientific literature relating to both the API and FPP should be included in  
2777 this section of the PD when appropriate.  
2778

## 2779 **5. REFERENCES**

- 2780 1. Guidelines on packaging for pharmaceutical products. In: *WHO Expert Committee on*  
2781 *Specifications for Pharmaceutical Preparations. Thirty-sixth report.* Geneva, World  
2782 Health Organization, 2002, Annex 9 (WHO Technical Report Series, No. 902)  
2783  
2784 2. Good manufacturing practices for sterile pharmaceutical products. In: *WHO Expert*  
2785 *Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report.*  
2786 Geneva, World Health Organization, 2002, Annex 6 (WHO Technical Report Series,  
2787 No. 902)  
2788  
2789 3. Good manufacturing practices for pharmaceutical products: main principles. In: *WHO*  
2790 *Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh*  
2791 *report.* Geneva, World Health Organization, 2003, Annex 4 (WHO Technical Report  
2792 Series, No. 908)  
2793  
2794 4. Recommendations on risk of transmitting animal spongiform encephalopathy agents  
2795 via medicinal products. In: *WHO Expert Committee on Specifications for*  
2796 *Pharmaceutical Preparations. Thirty-seventh report.* Geneva, World Health  
2797 Organization, 2003, Annex 1 (WHO Technical Report Series, No. 908)  
2798  
2799 5. Guidelines for registration of fixed-dose combination medicinal products. Appendix  
2800 3: Pharmaceutical development (or preformulation) studies. Table A1: Typical stress  
2801 conditions in preformulation stability studies. In: *WHO Expert Committee on*  
2802 *Specifications for Pharmaceutical Preparations. Thirty-ninth report.* Geneva, World  
2803 Health Organization, 2005, Annex 5 (WHO Technical Report Series, No. 929).  
2804  
2805 6. Multisource (generic) pharmaceutical products: guidelines on registration  
2806 requirements to establish interchangeability. In: *WHO Expert Committee on*  
2807 *Specifications for Pharmaceutical Preparations. Fortieth report.* Geneva, World  
2808 Health Organization, 2006, Annex 7 (WHO Technical Report Series, No. 937)

- 2809  
2810 7. General guidelines for the establishment, maintenance and distribution of chemical  
2811 reference substances. In: *WHO Expert Committee on Specifications for*  
2812 *Pharmaceutical Preparations. Forty-first report.* Geneva, World Health Organization,  
2813 2007, Annex 3 (WHO Technical Report Series, No. 943).  
2814
- 2815 8. Guidelines on active pharmaceutical ingredient master file procedure. In: *WHO Expert*  
2816 *Committee on Specifications for Pharmaceutical Preparations. Forty-second report.*  
2817 Geneva, World Health Organization, 2008, Annex 4 (WHO Technical Report Series,  
2818 No. 948).  
2819
- 2820 9. Stability testing of active pharmaceutical ingredients and finished pharmaceutical  
2821 products. In: *WHO Expert Committee on Specifications for Pharmaceutical*  
2822 *Preparations. Forty-third report.* Geneva, World Health Organization, 2009, Annex 2  
2823 (WHO Technical Report Series, No. 953)  
2824
- 2825 10. Procedure for prequalification of pharmaceutical products. In: *WHO Expert*  
2826 *Committee on Specifications for Pharmaceutical Preparations. Forty-third report.*  
2827 Geneva, World Health Organization, 2009, Annex 3 (WHO Technical Report Series,  
2828 No. 953)  
2829
- 2830 11. WHO good distribution practices for pharmaceutical products. In: *WHO Expert*  
2831 *Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report.*  
2832 Geneva, World Health Organization, 2010, Annex 5 (WHO Technical Report Series,  
2833 No. 957)  
2834

## Annex 1

### Recommendations for conducting and assessing comparative dissolution profiles

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

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

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

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

$$f_2 = 50 \text{ LOG } \{ [1 + 1/n \sum_{t=1}^n (R_t - T_t)^2]^{-0.5} \times 100 \}$$

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

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

- 2885
- 2886
- 2887
- 2888
- 2889
- 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.

Draft for comment

## Annex 2

### Product quality review requirements for *established multisource products*

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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.

\*\*\*