



**World Health  
Organization**

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3 **GUIDELINE ON SUBMISSION OF DOCUMENTATION FOR**  
4 **A MULTISOURCE (GENERIC) FINISHED**  
5 **PHARMACEUTICAL PRODUCT (FPP):**  
6 **PREPARATION OF PRODUCT DOSSIERS (PDS)**  
7 **IN COMMON TECHNICAL DOCUMENT (CTD) FORMAT**  
8

9 *DRAFT FOR COMMENT*  
10

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36 SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT  
37 QAS/10.375:  
38

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Any further action as required	...

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Draft for comment

69

## 70 1. INTRODUCTION

### 71 1.1 Background

72

73 WHO Technical Report Series, No. 953 (TRS No. 953), Annex 3 (2009) entitled *Procedure*  
74 *for Prequalification of Pharmaceutical Products* outlines the procedure and considerations for  
75 the process undertaken by WHO in providing United Nations agencies with advice on the  
76 acceptability in principle of pharmaceutical products for procurement by such agencies. TRS  
77 No. 953 states:

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

80 As mentioned in TRS No. 953, in submitting an expression of interest (EOI) for product  
81 evaluation, the applicant should send to the WHO focal point (together with the other data  
82 requirements) a *product dossier* (PD), in the format specified in the WHO guidance  
83 documents on submitting product data and information.

84

85 Through the International Conference on Harmonisation (ICH) process, considerable  
86 harmonization has been achieved on the organization of the registration documents with the  
87 issuance of the common technical document (CTD) guideline. This recommended format in  
88 the CTD guideline for registration applications has become widely accepted by regulatory  
89 authorities both within and beyond the ICH Regions.

90

91 This document, *Guideline on submission of documentation for a multisource (generic)*  
92 *finished pharmaceutical product (FPP): Preparation of product dossiers (PDs) in common*  
93 *technical document (CTD) format*, provides recommendations on the format and presentation  
94 for these types of PDs.

95

### 96 1.2 Objectives

97

98 This guideline is intended to:

99

- 100 • assist applicants on the preparation of PDs for multisource products by providing clear  
101 general guidance on the format of these dossiers;
- 102
- 103 • fully adopt the modular format of the CTD as developed by ICH; and
- 104
- 105 • provide guidance on the location of regional information (Module 1) and other general  
106 data requirements.
- 107

108

108 These measures are intended to promote effective and efficient processes for the development  
109 of these PDs and the subsequent assessment procedures.

110

### 111 1.3 Scope

112

113 This guideline applies to PDs for multisource pharmaceutical products containing existing  
114 active pharmaceutical ingredients (APIs) of synthetic or semi-synthetic origin and their  
115 corresponding finished pharmaceutical products (FPPs). For the purposes of this guideline,

116 an existing API is one that has been previously authorized through a finished product by a  
117 stringent regulatory authority<sup>1</sup>. APIs from fermentation, biological, biotechnological or  
118 herbal origin are covered by other guidelines.

119  
120 This guideline primarily addresses the organization of the information to be presented in PDs  
121 for multisource products. It is not intended to indicate what studies are required. It merely  
122 indicates an appropriate format for the data that have been acquired. Applicants should not  
123 modify the overall organization of the CTD as outlined in the guideline.

124

#### 125 1.4 General principles

126

127 This guideline presents the agreed upon common format for the preparation of a well  
128 structured CTD for PDs that will be submitted to WHO. A common format for the technical  
129 documentation will significantly reduce the time and resources needed to compile PDs for the  
130 prequalification of multisource pharmaceutical products and will ease the preparation of  
131 electronic submissions. Assessments and communication with the applicant will be facilitated  
132 by a standard document of common elements. In addition, exchange of regulatory information  
133 between national medicine regulatory authorities (NMRAs) and with WHO will be simplified.

134

135 Ultimately, this is intended to support the objectives of the Prequalification Programme in  
136 listing pharmaceutical products of acceptable safety, efficacy and quality in the interest of  
137 public health.

138

139 This *general filing guideline* should be read in conjunction with other applicable WHO and  
140 ICH reference documents and guidelines that provide further guidance and recommendations  
141 on the topic-specific content requirements for multisource products, notably:

142

- 143 • *Multisource (generic) pharmaceutical products: guidelines on registration*  
144 *requirements to establish interchangeability (TRS No. 937, Annex 7, 2006);*
- 145
- 146 • *Bioequivalence trial information form (BTIF);*
- 147
- 148 • *Guideline on submission of documentation for a multisource (generic) finished*  
149 *pharmaceutical product (FPP): quality part;*
- 150
- 151 • *Quality overall summary – product dossier (QOS-PD).*

152

153 Together these guidelines, templates and reference documents mentioned within are intended  
154 to assist applicants and WHO by harmonizing with international approaches and facilitating  
155 the preparation and subsequent assessment procedures for PDs through the integration of the  
156 internationally accepted CTD format and, where possible, terminology.

157

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<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](http://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 (may be updated from time to time).

158 Once implemented these guidelines will supersede the following guidelines and template  
159 which were in use prior to the development of this guideline:

160

161 • *Guideline on submission of documentation for prequalification of multi-source*  
162 *(generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS,*  
163 *malaria and tuberculosis;*

164

165 ○ *Supplement 1 - Dissolution testing;*

166 ○ *Supplement 2 - Extension of the WHO List of stable (not easily degradable*  
167 *ARV) APIs;*

168

169 • *Pharmaceutical quality information form (PQIF).*

170

## 171 2. GLOSSARY

172

173 *active pharmaceutical ingredient (API)*

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

179

180 *applicant*

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

185

186 *finished pharmaceutical product (FPP)*

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

190

191 *manufacturer*

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

194

195 *multisource (generic) pharmaceutical products*

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

199

## 200 3. ORGANIZATION OF A PRODUCT DOSSIER FOR A MULTISOURCE 201 PRODUCT IN CTD FORMAT

202

203 The CTD is organized into five *modules*. Module 1 is region-specific. Modules 2, 3, 4 and 5  
204 are intended to be common for all regions. Conformance with this guideline should ensure  
205 that these four modules are provided in a format acceptable to WHO and regulatory  
206 authorities.

207

208 This section provides an overview of module contents for a multisource product in greater  
209 detail.

210

- 211 • Module 1- Administrative information and prescribing information:
  - 212 ○ This module should contain documents specific to WHO and each region; for
  - 213 example, application forms or the proposed label for use in the region. The
  - 214 content and format of this module can be specified by WHO and the relevant
  - 215 regulatory authorities.
  - 216 ○ A summary of the bioequivalence/bioavailability information should be
  - 217 provided according to WHO's *Bioequivalence trial information form (BTIF)*.
  - 218 ○ Quality information summary (QIS) - see WHO's *Guideline on submission of*
  - 219 *documentation for a multisource (generic) finished pharmaceutical product*
  - 220 *(FPP): quality part* for instructions.
  - 221

- 222 • Module 2 - CTD summaries:

- 223 ○ This module should begin with a general introduction to the pharmaceutical,
- 224 including its pharmacological class, mode of action and proposed clinical use.
- 225 In general, the Introduction should not exceed one page.
- 226 ○ A summary of the quality information should be provided according to WHO's
- 227 *Quality overall summary – product dossier (QOS-PD)* template.
- 228 ○ The organization of these summaries is described in Guidelines for ICH M4Q,
- 229 M4S and M4E.
- 230

- 231 • Module 3 - Quality:

- 232 ○ Information on quality should be presented in the structured format described
- 233 in Guidelines ICH M4Q and WHO's *Guideline on submission of*
- 234 *documentation for a multisource (generic) finished pharmaceutical product*
- 235 *(FPP): quality part*.
- 236

- 237 • Module 4 - Nonclinical study reports:

- 238 ○ Generally not applicable for multisource products (some exceptions may
- 239 apply).
- 240

- 241 • Module 5 - Clinical study reports:

- 242 ○ The human study reports and related information should be presented in the
- 243 order described in Guidelines ICH M4E and WHO's *Multisource (generic)*
- 244 *pharmaceutical products: guidelines on registration requirements to establish*
- 245 *interchangeability*.
- 246

247 The overall organization of the CTD is presented in the following diagram.

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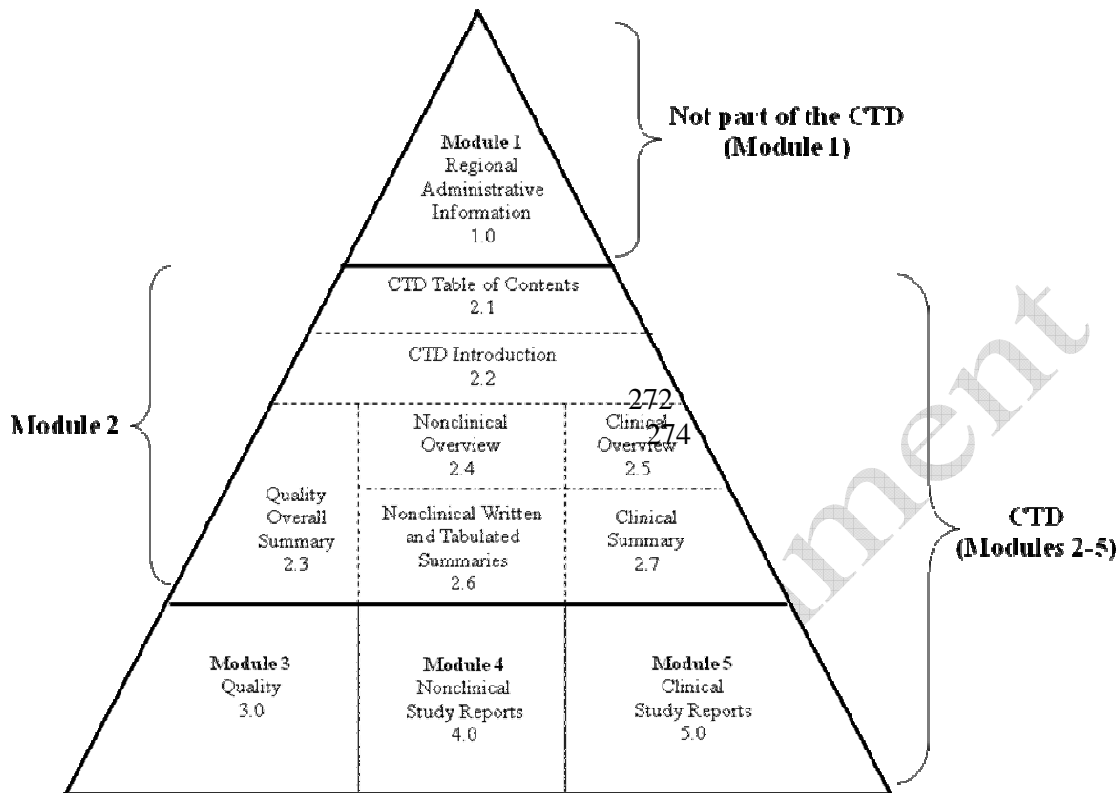
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In preparing PDs for multisource products, it is acknowledged that certain modules or sections of the CTD would generally *not be applicable* (e.g. Module 4 – nonclinical study reports, although some exceptions may apply) and should be marked as such.

#### 4. MODULES (INCLUDING MODULE 1) OF A PRODUCT DOSSIER FOR A MULTISOURCE PHARMACEUTICAL PRODUCT

This section outlines filing considerations for PDs in the CTD format. Table 1 below provides an overview of the presentation of the PD, including modular structure and main headings.

**Table 1:** Modular format of PDs for multisource products in CTD format:

<b>Module 1 – Administrative information and prescribing information</b>
1.0 Cover letter
1.1 Table of contents of the application including Module 1 (Modules 1-5)
1.2 Application information:
1.2.1 Copy of the expression of interest (EOI)
1.2.2 Manufacturing and marketing authorization(s)/international registration status and/or the WHO certificate of pharmaceutical product (CPP)
1.2.3 Copy of certificate(s) of suitability of the European Pharmacopoeia (CEP) (including any annexes)
1.2.4 Letters of access for APIMFs
1.2.5 Good manufacturing practices (GMP) information
1.2.6 Biowaiver requests in relation to conducting a comparative

bioavailability study
1.3 Product information:
1.3.1 Summary of product characteristics (SmPC)
1.3.2 Labelling (outer and inner labels)
1.3.3 Package leaflet (also known as patient information leaflet or PIL)
1.4 Regional summaries:
1.4.1 Bioequivalence trial information form (BTIF)
1.4.2 Quality information summary (QIS)
1.5 Electronic review documents (e.g. product information, BTIF, QIS, QOS-PD)
1.6 Samples (e.g. FPP, device(s), certificates of analysis)
<b>Module 2 – Common technical document (CTD) summaries</b>
2.1 CTD Table of contents (Modules 2-5)
2.2 CTD Introduction
2.3 Quality overall summary – product dossier (QOS-PD)
2.4 Nonclinical overview – generally not applicable for multisource products (some exceptions may apply)
2.5 Clinical overview
2.6 Nonclinical written and tabulated summaries – generally not applicable for multisource products (some exceptions may apply)
2.7 Clinical summary – generally not applicable for multisource products
<b>Module 3 – Quality</b>
3.1 Table of contents of Module 3
3.2 Body of data
3.3 Literature references
<b>Module 4 – Nonclinical study reports</b> – generally not applicable for multisource products (some exceptions may apply)
4.1 Table of contents of Module 4
4.2 Study reports
4.3 Literature references
<b>Module 5 – Clinical study reports</b>
5.1 Table of contents of Module 5
5.2 Tabular listing of all clinical studies
5.3 Clinical study reports
5.3.1 Reports of biopharmaceutical studies
5.3.7 Case report forms and individual patient listings
5.4 Literature references

309

310 Additional guidance for some of the sections to be included in Module 1 is provided below:

311

312 *1.0 Cover letter*

313

314 The covering letter submitted with the PD should include a clear statement by the responsible  
315 person submitting the PD, indicating that the information submitted is true and correct.

316

317 *1.2.2 Manufacturing and marketing authorization(s)/international registration status*

318

319 List the countries in which:

320

321     • the FPP (or set of FPPs) has been granted a marketing authorization;

- 322       • the FPP (or one or more of the set of FPPs) has been withdrawn from the market; and  
323       • an application for the marketing of the FPP (or one or more of the set of FPPs) has  
324       been rejected, deferred or withdrawn  
325

326 For further guidance see Section 3.2.P.3.1 of the *Guideline on submission of documentation*  
327 *for a multisource (generic) finished pharmaceutical product (FPP): quality part*.  
328

#### 329 *1.4 Regional summaries*

330

331 The regional summaries should be prepared in accordance with the available WHO templates,  
332 which are available on the WHO Prequalification website.  
333

#### 334 *1.5 Electronic review documents*

335

336 Electronic submission of documentation (CD or DVD) should be submitted in Microsoft  
337 Word.  
338

#### 339 *1.6 Samples (e.g. FPP, device(s))*

340

341 A sample and certificate of analysis should be provided of the FPP(s) and devices(s) to enable  
342 visual inspection of the pharmaceutical product, the packaging materials and the label as well  
343 as comparison of the data with those in the SmPC, labelling and the package leaflet.  
344

345 Draft labelling may be submitted at the time of dossier submission when labelling for  
346 marketing has not been finalized. For guidance regarding labelling, refer to the information  
347 available on WHO public assessment reports (WHOPARs) available on the Prequalification  
348 website under Information for Applicants (Prequalification Guidelines).  
349

### 350 **5. MODULE 3 - QUALITY**

351

352 For Module 3.2.S Drug substance (or active pharmaceutical ingredient (API)), there are three  
353 options to satisfy the information requirements for APIs within the Prequalification  
354 Programme. In brief these are:  
355

- 356       • Option 1: certificate of suitability of the European Pharmacopoeia (CEP) procedure;  
357       • Option 2: active pharmaceutical ingredient master file (APIMF) procedure; or  
358       • Option 3: full details in the PD.  
359

360 All options require the submission of information in CTD format (3.2.S), although the  
361 content may differ in places. The document *Guideline on submission of documentation for a*  
362 *multisource (generic) finished pharmaceutical product (FPP): quality part* provides detailed  
363 guidance on this issue and on the preparation of the FPP information by the applicant.  
364

### 365 **6. MODULE 5 OF A PRODUCT DOSSIER FOR A MULTISOURCE** 366 **PHARMACEUTICAL PRODUCT**

367

368 The majority of PDs for multisource products are supported by one or more pivotal  
369 comparative bioavailability studies. When filing a PD in the CTD format, it is anticipated that  
370 only the following relevant sections of Module 5 will normally be required.  
371

372 Module 5: Clinical study reports

373

- 374 • 5.1 Table of contents for Module 5
- 375 • 5.2 Tabular listing of all clinical studies
- 376 • 5.3 Clinical study reports
- 377 ○ 5.3.1 Reports of biopharmaceutical studies
- 378 ■ 5.3.1.2 Comparative bioavailability and bioequivalence study reports
- 379 ■ 5.3.1.3 In vitro-in vivo correlation study reports
- 380 ■ \*5.3.1.4 Reports of bioanalytical and analytical method for human
- 381 studies
- 382 ○ 5.3.7 Case report forms and individual patient listings
- 383 • 5.4 Literature references

384

385

386

387

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\* Bioanalytical or analytical methods for BA/BE or in vitro dissolution studies should ordinarily be provided in the individual clinical study reports. However, where a method is used in multiple studies, the method and its validation should only be included once in section 5.3.1.4 and referenced in the appropriate individual clinical study reports.

390

391

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393

394

For guidance regarding biowaivers, refer to the biowaiver implementation documents available on the Prequalification website. For guidance regarding comparator products, refer to the information available under Guidance on Bioequivalence Studies on the Prequalification website.

395

396

397

## 7. GUIDANCE ON FORMAT AND PRESENTATION OF A PRODUCT DOSSIER IN CTD FORMAT

398

399

### 7.1 Guidance on format

400

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Throughout the CTD, the display of information should be unambiguous and transparent. Text and tables should be prepared using margins that allow the document to be printed on both A4 paper (EU and Japan) and 8.5 x 11" paper (US). The left-hand margin should be sufficiently large that information is not obscured by the method of binding. Font sizes for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying. Times New Roman, 12-point font, is recommended for narrative text.

407

408

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Acronyms and abbreviations should be defined the first time they are used in each module.

References should be cited in accordance with the current edition of the *Uniform requirements for manuscripts submitted to biomedical journals*, International Committee of Medical Journal Editors (ICMJE)<sup>2</sup>. Copies of relevant pages of references should be provided, with a copy of the full article in the case of a publication. English translations should be provided as necessary.

415

416

417

418

### 7.2 Guidance on presentation

The paper copies of the application should be bound for easy access of information.

418

---

<sup>2</sup> The first edition of the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* was conceived by the Vancouver Group and was published in 1979.

419 Each binder should be labelled with the proprietary name and the non-proprietary name of the  
420 FPP (e.g. “Name ABC” Abacavir (as sulfate) 300 mg Tablets) and the company name of the  
421 applicant. For ease of reference, the following information could also be included on the label  
422 of each binder (space permitting): the volume number for that binder (out of the total number  
423 of volumes *for that module*), the section(s) contained within each volume and the date of the  
424 application (month and year), e.g.

425  
426 FPP “Name ABC”  
427 Nonproprietary name  
428 Applicant “XYZ”  
429 Module 3 - Quality  
430 Volume 1 of 3  
431 Mod. 3.1 - 3.2.S.3  
432 Month/year  
433

## 434 8. VARIATIONS

435

436 All variation applications should be submitted using the CTD format, regardless of the  
437 original PD format.

438

439 In the case of the filing of a variation, applicants would normally provide only the relevant  
440 modules or sections affected by the change. For example, if the variation was for a change in  
441 the shelf-life of the FPP, only those sections affected by the change would need to be  
442 submitted.

443

444 An updated and annotated QIS should be provided with each variation application.

445

## 446 9. REFERENCES

- 447 1. Organization of the Common Technical Document for the Registration of  
448 Pharmaceuticals for Human Use (ICH M4)  
449
- 450 2. The Common Technical Document for the Registration of Pharmaceuticals for Human  
451 Use: Quality (ICH M4Q)  
452
- 453 3. The Common Technical Document for the Registration of Pharmaceuticals for Human  
454 Use: Safety (ICH M4S)  
455
- 456 4. The Common Technical Document for the Registration of Pharmaceuticals for Human  
457 Use: Efficacy (ICH M4E)  
458  
459 together with the complementary ICH Questions and Answers documents for the  
460 above mentioned guidelines.  
461
- 462 5. Multisource (generic) pharmaceutical products: guidelines on registration  
463 requirements to establish interchangeability In: *WHO Expert Committee on  
464 Specifications for Pharmaceutical Preparations. Fortieth report*. Geneva, World  
465 Health Organization, 2006, Annex 7 (WHO Technical Report Series, No. 937).  
466
- 467 6. Stability testing of active pharmaceutical ingredients and finished pharmaceutical  
468 products In: *WHO Expert Committee on Specifications for Pharmaceutical*

