



TECHNICAL REQUIREMENTS FOR PHARMACEUTICAL PRODUCTS

3rd Edition November 2009



unite for
children



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INTRODUCTION

General information

The technical requirements described in this document complement, and should be used together with, the UNICEF general item descriptions as they are provided in bid documents. The purpose is to provide further general technical guidance to bidders and suppliers on UNICEF's expectations of quality, safety and efficacy for pharmaceuticals that are procured for global distribution.

Questionnaires

These technical requirements specify information to be given by bidders/suppliers when completing documents requested for bidding purposes.

UNICEF is currently using the following questionnaires, which must be signed, dated and submitted as specified in the bid documents.

- UNICEF Technical Questionnaire for Pharmaceutical Manufacturers
- Inter Agency Pharmaceutical Product Questionnaire (or its equivalent)

SECTION 1 - FINISHED PHARMACEUTICAL PRODUCT

Regulatory requirements

All Finished Pharmaceutical Products (FPPs) should have evidence of registration/marketing authorisation in the country of manufacture/origin. A marketing authorisation from a stringent regulatory authority (SRA), as defined by the World Health Organization (WHO), is desired.

All FPPs should have a Certificate of Pharmaceutical Product (CPP) according to the WHO Certification Scheme, or an equivalent, issued by the National Regulatory Authorities and specified in the relevant WHO Technical Report Series

Identification

Each FPP must be identified by the International Non-proprietary Name (INN) thus:

1. The Active Pharmaceutical Ingredient (API) base or the prodrug compound, salt or ester, as applicable.
2. The pharmaceutical dosage form – see Annex 1 for examples.
3. The amount of active ingredient in each unit dosage form; where this is given in terms of the salt, ester or prodrug, the equivalent amount of active moiety must be specified.
4. Route of administration.
5. Inactive ingredients/excipients of medical and/or pharmaceutical relevance and the amount in each dosage unit.

Bidders must submit the complete qualitative and quantitative composition of the FPP, including active ingredient(s) and excipients.

Monograph specifications

UNICEF accepts the following pharmacopoeial monographs: The British Pharmacopoeia (BP), European Pharmacopoeia (Ph.Eur), International Pharmacopoeia (Ph.Int) or United States Pharmacopoeia (USP). Whenever used, the year of publishing of the pharmacopoeia must be specified.

If there is no monograph, in-house specifications and validated analytical test methods must be submitted. They must be described in sufficient detail to enable the procedures to be repeated, including biological and microbiological methods where relevant. The results of validation studies, including comments on the choice of routine tests and standards must be submitted as well.

For all FPPs copies of certificates of analysis for the last three production batches are required.

General requirements for dosage forms

Each FPP should comply with the general requirements for dosage forms of the relevant edition of BP, Ph.Eur, Ph.Int or USP. At the minimum, all dosage forms must be packed:

1. So as to facilitate course-of-therapy usage, unless specified otherwise.
2. Together with dose measurement and delivery devices as applicable.
3. In tamper-evident packaging.
4. In rigid paperboard boxes, strong enough to resist crushing during transportation and storage.

Packaging

A primary package is that which is in direct contact with the dosage form.

A secondary package is not directly in contact with the dosage form. All packaging must be designed so as to protect the dosage form and to render it suitable for the intended use throughout the stated shelf life.

1. Materials used for packaging must conform to the relevant edition of the BP, USP, Ph.Eur or Ph.Int with reference to the specific Active Pharmaceutical Ingredient (API) and dosage form; must be safe for use with the dosage form for the intended route of administration; and be suitable for shipment, storage and worldwide use at extreme temperatures and humidity¹.
2. Packaging must facilitate the distribution to the lowest level health facilities as well as dispensing to individual patients and their subsequent adherence. Product packaging that facilitates patient adherence is encouraged.
3. The size of the container should be proportional to its contents with the addition of appropriate padding to prevent damage to the product during shipment.
4. Glass containers will not be accepted above a maximum of 250 ml. Glass bottles must be separated by criss-cross partitions or be packed individually in cartons.
5. For glass ampoules, single ended, break-off necks are required.

Labels

Language

English and/or French. Bidders should be prepared to include other language requirements for specific orders.

Type

Preferably by lithography direct on container/packaging.

Self-adhesive labels should use pharmaceutical defiberised paper (80g/kvm) that is film or UV coated for protection against humidity and be firmly affixed to be tamper proof and to prevent detachment in tropical climates.

Ink/colour

The writing on primary and secondary packs must be in indelible ink, preferably in black on white.

Minimum information required on labels

The following label information is mandatory for FPPs to be supplied for and on behalf of UNICEF:

1. International Non-proprietary Name (INN) or generic name of the FPP, in a bold, clearly visible font size. INNs must not be abbreviated anywhere, including on labels and package inserts.
2. Amount of API or active moiety per dosage unit, unit of volume or unit of weight.
3. Names and amounts of excipients of medical and/or pharmaceutical relevance, e.g. "contains 10% ethanol". Other examples of excipients include: gluten, metabisulfite, parabens and

¹ More Information about Climatic Zones can be found on the official web site of the 'International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use' (ICH)
<<http://www.ich.org/cache/compo/276-254-1.html>>

tartrazine. If the medicinal product is a parenteral, topical, inhalational or an eye preparation, all excipients must be stated.

4. Pharmaceutical dosage form. The pharmacopoeial standard of the FPP; and where not available, as with innovator products, the source of the reference standard must be available on request.
5. Net quantity per unit pack labelled on that unit pack (primary, secondary, tertiary) in a visible manner.
6. Directions for use.
7. Any special instructions for use e.g. "to be swallowed whole - do not chew".
8. Recommended temperature and humidity during transport and storage.
9. Special storage and handling instructions, including warnings and precautions.
10. If a product has a limited shelf life after the primary package is opened and manipulated, this should be indicated on the label.
11. Batch identification.
12. Manufacture date.
13. Expiry date in a format that can be easily understood. The recommended format is DD/MM/YYYY. The year of expiry must be 4 digits.
14. Name and address of manufacturer and marketing authorisation holder. For contract manufacture, indicate as: manufactured by company X for company Y.

Layout of information on labels

1. Information 1-6 above (minimum information on labels) should appear clearly and adjacent to each other.
2. The strength of the API should at all times appear next to the name of the API, e.g. Artemether 20mg + Lumefantrine 120mg.
3. Components in Fixed dose combination FPPs (FDCs) and copacks should be written in ascending alphabetical order with reference to the first letter of the INN e.g. Artemether 20mg + Lumefantrine 120mg.
4. Co-formulated FDC products, should be denoted with a "+" or "/" sign e.g. Artemether 20mg + Lumefantrine 120mg, while co-packaged FDCs should be denoted with an "&" sign e.g. Amodiaquine 153mg & Artesunate 50mg
5. The design of the secondary packaging label, and where applicable, the primary packaging label, must allow for the writing of dispensing information or addition of labels without covering important information on the manufacturer label.

This desired label format is expected at the time of supply, subject to acceptable variations according to each order. The bidder is expected to confirm that they are able to do such labelling, should their samples submitted for technical evaluation be different.

Summary of product characteristics and package inserts/patient information leaflets

The summary of product characteristics (SPC) as well as a detailed pack insert/patient information leaflet (PIL) as per standards and norms for each FPP must be submitted.

Suitability of brand names or registered trade names

UNICEF prefers that ONLY the International Non-proprietary Name (INN) is written on all labels and pack inserts and that any proprietary, brand or registered trade name is not included. If included, it must not be so prominent as to mask the appearance and readability of the INN.

Stability²

1. Accelerated stability studies, as defined by WHO, should be carried out for six months on at least three primary batches. One of the three batches should be of production scale and the other two should be at least of pilot scale. This is compulsory for FDC products and new APIs.
2. Real time stability studies as defined by the WHO guidelines should be carried out for at least three primary batches. One of the three batches should be of production scale and the other two should be at least of pilot scale.
3. Stability data reported should cover the entire shelf life as allocated to the FPP. For example, a 24 month shelf life can be covered by satisfactory 12 month real time and 6 month accelerated stability study data. For a product that contains stable API as listed in Supplement 2 of WHO generic guidelines, 24 month shelf life is covered by 6 month satisfactory real time and 6 months satisfactory accelerated stability data.
4. The specifications and methods used during stability studies must be described. If this is identical to a methodology described elsewhere in the data set, a cross-reference will suffice. If a different methodology was used, the test procedures applied to the stability tests on the FPP should be validated or verified, and the accuracy as well as the precision (standard deviations) should be recorded. Specific methods, such as high-performance liquid chromatography (HPLC) or gas chromatography (GC), must be used for the assay and determination of degradation products.
5. For all stability studies, numerical values of results must be stated, the word "complies" or "conforms" will not be acceptable in place of numerical values.
6. A full stability report, including trend graphs of all relevant parameters and analyses and discussion of results, should be presented. Shelf life conclusions should be drawn therein.
7. Where the product is to be reconstituted and/or diluted before use, such as powder or concentrate for injection or a powder for oral suspension "in use" stability data must be submitted to support the recommended in-use storage conditions and duration.

Shelf life and Storage

1. The assigned shelf life and recommended storage conditions should reflect the outcome of stability studies, as per WHO guidelines and be printed on labels and leaflets. Acceptable temperature excursions should be specified.
2. The bidder is responsible to inform UNICEF if special transport and packaging is required for a product, such as cold storage.

Pharmaceutical equivalence

The results of pharmaceutical equivalence studies, where applicable, should be submitted as outlined in the interagency pharmaceutical product questionnaire or its equivalent. These include bioequivalence studies and bioavailability studies such as dissolution and comparative dissolution profiles.

Pharmaceutical equivalence studies are not required for formulations that are WHO prequalified.³

² For detailed requirements see World Health Organisation, *WHO Expert Committee on Specifications for Pharmaceutical Preparations*, 43rd Report, Geneva, 2009, Annex 2: Stability testing of active pharmaceutical ingredients and finished pharmaceutical products.
<http://www.who.int/medicines/publications/pharmprep/PDF_TRS953_WEB.pdf>

³ The United Nations Prequalification Programme, managed by WHO: <<http://apps.who.int/prequal/>>

SECTION 2 - ACTIVE PHARMACEUTICAL INGREDIENT(S) AND EXCIPIENTS

1. API's and excipients should comply with the current requirements of the, British (BP), European (Ph.Eur), International (Ph.Int) and/or United States (USP) Pharmacopoeias. If not described in a pharmacopoeia, a copy of the manufacturer's specification, the certificate of analysis and a description of the test methods with limits for results must be submitted.
2. A confirmatory certificate of analysis from the API supplier should be available at least for the duration of the shelf life of all batches of FPP in which the API and excipients are used, and the certificate should be satisfactory as defined in WHO's Good Manufacturing Practice (GMP) guidelines⁴.
3. Site(s) of manufacture of API and/or Intermediates such as granulates, as well as any alternative manufacturers should be listed.
4. A GMP certificate of the API manufacture site(s) must be submitted
5. A copy of a valid Certificate of Suitability to the European Pharmacopoeia (CEP) **and/or evidence**, that the open part of a Drug Master File (DMF) for the APIs and excipients used is filed, must be provided.
6. UNICEF should be notified and approve of any changes in API sources, routes of synthesis and/or specifications.

SECTION 3 - MANUFACTURING STANDARDS

Good Manufacturing Practice

Both APIs and FPPs must be manufactured as per GMP guidelines established by WHO.⁵

Manufacturing site(s)

UNICEF must approve the site(s) of manufacture and UNICEF must also approve any changes in manufacturing site(s).

The manufacturing site(s) where any aspect of manufacture occurs must be stated. This includes production, sterilisation, packaging and quality control. The bidder must submit a copy of the valid Manufacturing Licence for the site where the FPPs of interest are manufactured as issued by the relevant authorities in the country of manufacture, stating the dosage forms authorised for manufacture at the respective site.

Bidders may be required to submit a copy of the last inspection report by the National Regulatory Authority and/or other stringent regulatory authorities/international organizations, relevant to the manufacturing site. If the report is considered confidential, UNICEF will accept a summary of the key positive and negative aspects provided that contact details of a contact person from the inspecting authority/agency, who can corroborate the information contained therein, are provided and that the detailed report can be made available under confidential cover for review on request.

Contract manufacture

UNICEF must approve the site(s) of contract manufacture(s) and any changes thereof.

⁴ More information about GMP guidelines and Quality assurance systems can be found on the WHO website under <http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/index.html>

⁵ World Health Organisation, *Quality Assurance of Pharmaceuticals. A compendium of guidelines and related materials*. WHO, Geneva, 2007, Volume 2, 2nd updated edition or latest edition <<http://www.who.int/medicinedocs/index/assoc/s14136e/s14136e.pdf>>

Inspection

As UNICEF must approve the site(s) of manufacture, any successful bidder shall permit UNICEF, or any other representative as may be designated by UNICEF, to have access to the manufacturing facilities of the FPPs at all reasonable times to inspect the manufacturing site and processes for the production, quality control, quality assurance and packing. The bidder and/or manufacturer shall provide reasonable assistance to UNICEF or any other representative as may be designated by UNICEF for such appraisal, including copies of any documentation as may be necessary. The inspection may be carried out in conjunction with the relevant National Regulatory Authority.

SECTION 4 – COMMITMENT

The manufacturer shall inform UNICEF immediately about any serious quality and/or safety concerns related to the manufacture, control or use of their product, including suspension or cancellation of marketing authorisations.

The manufacturer pledges to work with UNICEF to minimise potential public health risks by actively organizing product recalls of defective products and either in replacing the defective product or covering the direct and related costs related to replacing the defective product within defined timelines as specified in the contractual requirements.

ANNEX 1

Descriptions of a selection of pharmaceutical dosage forms

Note: These descriptions are not exhaustive

<ul style="list-style-type: none">□ Tablets<ul style="list-style-type: none">○ Scored○ Solid○ Dispersible○ Chewable○ Buffered (Specify buffers)○ Film coated○ Enteric coated○ Sublingual○ Bilayered○ Delayed release○ Controlled release	<ul style="list-style-type: none">□ Capsules<ul style="list-style-type: none">○ Enteric coated○ Delayed release○ Controlled release○ Sublingual○ Other (Specify)□ Oral liquids<ul style="list-style-type: none">○ Solution○ Suspension○ Powder for liquid○ Powder for suspension
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ANNEX 2

How to submit documentation for UNICEF bid exercises

The technical requirements apply to all UNICEF procurement solicitation modalities

- Request for Expression of Interest (REOI)
- Invitation to Bid (ITB)
- Request for Quotation (RFQ)
- Request for Proposal (RFP)

They are also relevant to UNICEF contractual instruments

- Long Term Arrangements (LTAs)
- Purchase Orders (POs)

Documents that are not originally in English MUST be accompanied by an accurate professional English translation and certified as a true translation of the original.

Documents may be submitted in suitable **electronic formats** as indicated with each solicitation or contractual modality.

1. Each **electronic or physical paper file** must have the following information on the front page
 - 1.1. The solicitation reference number
 - 1.2. The file reference number as outlined below
 - 1.3. The complete FPP description. .
 - 1.4. Bidder and/or manufacturer name and contact details.
 - 1.5. The words "DOCUMENTS FOR TECHNICAL EVALUATION"
2. Each **electronic or physical paper file** must have a table of contents.
3. Each **physical paper file must have** unique identifiers/separators so as to enable easy location of the relevant document in the file.
4. All documents submitted must be typed in readable font type and size in black on white and duly signed. No handwritten documents will be accepted
 - 1.1. Font type: Times New Roman or Verdana preferred
 - 1.2. Font size: Minimum 10, Maximum 14
5. All documents or filled forms shall have no interlineations, erasures, or overwriting. If necessary to correct errors made by the bidder, such corrections shall be initialled by the person or persons signing the bid.
6. The bidder is responsible to ensure that any documents not requested or not listed below, but are required or would add value to the technical evaluation are submitted as an additional file (File 4 - Additional documents).

Content of documentation files

File 1 of 3:	Manufacturer Documentation
File 2 of 3 - Section one:	FPP, API and excipients Documentation
File 2 of 3 - Section two:	Packaging, Container/closure system(s)
File 3 of 3:	Documents to accompany samples

File 1 of 3: Manufacturer Documentation

1. Manufacturing licence(s).
2. Certified copy of valid and current WHO type GMP certificate.
3. Copy of last inspection report relevant to the manufacturing site.

File 2 of 3: How to submit Finished Pharmaceutical Product (FPP) documentation

1. Submit a separate complete file/binder for each FPP. An FPP is considered a separate product if it has its own Certificate of Pharmaceutical Product (CPP) issued by a National Regulatory Authority.
2. Label each file/binder in a logical sequence e.g. File 2a of 3 is for product A, which refers to the FPP with the lowest INN alphabetical ranking in the list of products quoted, File 2b of 3 is for product B, which refers to the FPP with the next ascending INN alphabetical ranking in the list of products quoted, after product A.
3. Files for FPPs containing the same API must be delivered in a sequence following each other to facilitate ease of cross reference.

File 2 of 3 - Section one: FPP, API and excipients Documentation – List of documents to provide

1. Formulation of the product (complete qualitative and quantitative composition including active ingredient(s) and excipients).
2. Flow diagram describing the manufacturing and control processes with relevant parameters.
3. Certificate of Pharmaceutical Product (CPP) according to the WHO Certification Scheme.
4. Copy of the relevant WHO Pre-qualification approval letter signed by your company.
5. WHO acceptance letter for product dossier review mentioning the WHO reference number assigned by WHO for this specific product.
6. Copy of internal finished product specifications.
7. Copy of the certificate of analysis for the 3 last batches released.
8. Validated analytical methods if specifications for finished product are in house specifications, different from BP, USP and Ph.Int.
9. Protocol and report for accelerated and real time stability testing.
10. Sample of the finished product(s) offered.
11. Packaging and label artwork.
12. Package insert/leaflet.
13. Copy of the report of the proof of therapeutic equivalence (BE study, comparative dissolution profile, dissolution tests, other).
14. GMP certificate(s) of API manufacturing site.
15. Copy of internal API specifications.
16. Validated analytical methods in case of in house API specifications.
17. Copy of the certificate(s) of analysis of the API from the API manufacturer as well as from the FP manufacturer.
18. Copy of the Certificate of suitability to the European Pharmacopoeia CEP and its annexes **and/or evidence** that the open part of the drug master file (DMF) for the APIs and excipients used is filed.
19. Evidence of product registration or marketing authorisation in country of manufacture/origin where applicable.
20. List of other countries where the product is registered, giving licence number, registration date and validity period.

File 2 of 3 - Section two: Packaging, Container/closure system(s)

1. Description and composition of the primary packaging.
2. Description and composition of the container/closure systems.
3. Description and composition of the liner/wadding/padding system.
4. Description and composition of secondary and any other packaging.
5. Evidence of conformance with the provisions of the relevant latest edition of the BP, USP, Ph.Eur. or Ph.Int.
6. Evidence of compliance with the requirement for packaging to be suitable for delivery and use in Zone IV A and B countries.

File 3 of 3: Documents to accompany samples

1. Package insert in English and/or French as specified.
2. Certificates of Analysis (for technical evaluation purposes), relevant to the sample, including specifications of the FPP at the time of batch release, and results of the full analysis of the batch in question. The certificate of analysis should include:
 - INN/Generic name of FPP
 - Dosage form and strength
 - Brand name of product
 - Manufacturer name, site and address
 - Pharmacopoeia reference (if applicable)
 - Contents per pack size
 - Description of physical characteristics
 - Batch identification
 - Batch quantity
 - Date of manufacture
 - Expiry date (dd/mm/YYYY)
 - Date of test (dd/mm/yyyy)
 - Actual test protocols, results and limits.

ANNEX 3

How to submit samples for technical evaluation

Bidders may be required to submit a specified number of non-returnable samples for each FPP. Please do not submit more samples than requested. Samples submitted should be in their final status and packaging as intended to be supplied on purchase orders. Samples will normally be accepted up to one week after the solicitation closes.

Requirements

1. For solid oral dosage forms with several pack sizes:
 - Submit the lowest pack size as a complete and intact sample.
 - Submit subsequent pack sizes within the correct primary and secondary packaging, including package insert, but with only the same number of dosage units as in the lowest pack size.
2. For parenteral and rectal preparations, submit a minimum of 5 and maximum of 10 individual units in the correct primary and secondary package and with package insert.
3. For powders for oral use and oral liquids, submit two (2) bottles/packs.

NOTE: UNICEF Supply Division⁶ is a big organization that regularly requests and receives samples from a variety of bidders. It is VERY IMPORTANT for the bidder to ensure that packages containing samples are **addressed correctly with the correct reference** to make sure they are delivered in time to the right person and physical location within UNICEF Supply Division.

⁶ <http://www.unicef.org/supply/index.html>