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Supply Division

Technical Requirements For Pharmaceutical and Nutrition Products

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Contents

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INTRODUCTION

General information

UNICEF seeks to provide timely access to affordable medicines and nutrition products that are safe, efficacious and of good quality in both development and humanitarian emergency contexts. Our product range is designed to meet global demand for key health and nutritional interventions and can be tailored for specific country/partner needs to optimize programme success. In principle, UNICEF products are aligned with normative standards and guidelines and designed to facilitate rational use to the lowest level of health care service delivery. WHO Model of Essential medicines List (EML) and disease specific treatment guidelines inform UNICEF product selection. WHO technical guidance informs specifications and requirements for procured products, including non-standard items.

Quality assessement is done principally via technical assessment of pharmaceutical product dossiers, samples and manufacturer Good Manufacturing Practices (GMP).

Technical information required for technical evaluation is collected through the **Interagency Finished Pharmaceutical Product Questionnaire (IAFPPQ)** which is based on the World Health Organization (WHO) Model quality assurance system for procurement agencies (MQAS) Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS986annex3.pdf?ua=1

Manufacturer GMP related information is collected through the UNICEF Technical Questionnaire for Pharmaceutical Manufacturers.

This technical requirements document provides further explanations to what is described in the most recent version of the IAFPPQ (https://www.unicef.org/supply/index_52844.html). It captures specifications and requirements that apply in general to every pharmaceutical product or dosage form. Specifications unique to a product are elaborated in each solicitation activity, Long Term Arrangement Contract and Purchase Order. Vendors are reminded to pay close attention to both unique specifications for each product and the general requirements in this document as they complement each other.

This document and all other related information for pharmaceuticals and nutrition[1] products, including questionnaires, can be accessed at any time at http://www.unicef.org/supply/index_52844.html

Vendors are encouraged to carefully read these documents well and seek clarifications in advance of any solicitation/tender process.

While this document details ALL general technical requirements, there may be variations of type/number of documents to be submitted with each solicitation/purchase order with respect to:

1. Multisource (generic) finished pharmaceutical products (FPPs) not approved by Stringent Regulatory Authorities (SRAs);
2. Multisource (generic) FPPs approved by SRAs;
3. Innovator FPPs approved by SRAs;
4. Any of the above products supplied through a wholesale or distributor or agent.

[1] Pharmaceutical vitamin and mineral products designed to prevent and/or treat single nutrient deficiencies

SECTION 1 - GENERAL INFORMATION

Product identification

Each FPP must be fully identified as stipulated in the most current version of the Interagency Finished Pharmaceutical Product Questionnaire (https://www.unicef.org/supply/index_52844.html), with the following additional explanations:

1. Products should be identified by their International Non-proprietary Names (INN). Generic name(s), British Approved Names (BAN) or others should be stated if different from INN;
2. The Active Pharmaceutical Ingredient(s) (API) should be stated as base, salt, ester or pro-drug compound as applicable;
3. Trade (proprietary) name(s) (if any). UNICEF does not recommend use of trade names and does not approve the same. Information is collected for technical evaluation purposes;
4. Vendor should include relevant pharmaceutical dosage form and dosage form attributes e.g. if tablets are functionally scored, dispersible, enteric coated, bilayered, film coated, sugar coated;
5. Specify the strength per dosage unit or the amount of active ingredient per dosage unit. Where this is given in terms of the salt, ester or pro-drug, the equivalent amount of active moiety must be specified; further described in WHO TSR 957 (p62) 2010 - http://www.who.int/medicines/publications/pharmprep/en/index.html
6. Specify the route of administration e.g. IM, IV, SC, PO, rectal;
7. Specify inactive ingredients and/or excipients of medical/ pharmaceutical relevance, amount in the dosage form or per dosage unit e.g. contains Alcohol 10%;
8. Mention if product is fixed-dose combination (FDC) e.g. co-pack/co-blister, co-formulated.

Packaging

See Container-closure systems

Regulatory (Licensing) status

All Finished Pharmaceutical Products (FPPs) should have evidence that product is registered/licensed in the country of manufacture/origin. Where product is registered in the country of manufacture/origin, vendor must indicate whether the product is actually marketed in that country or registered for EXPORT ONLY.

Vendor should list other countries where product is registered, including respective license numbers and validity period. Registration in countries where UNICEF supplies will be sent is important. The countries can be identified from the forecasting information or as specified in the solicitation document.

Vendors must submit a Certificate of Pharmaceutical Product (CoPP or CPP) for each FPP according to the WHO Certification Scheme, or an equivalent, issued by the National Regulatory Authority in the country of manufacture/origin. Recommended CoPP/CPP format is specified in the relevant WHO Technical Report Series (WHO TRS 863, earlier versions not acceptable). The CoPP required for tender technical evaluation can be for any country. Specific country CoPPs may be required and requested during the procurement process.

Pharmacopoeial standards

UNICEF accepts the following pharmacopoeias with reference to specifications, qualitative and quantitative composition, quality standards, identification and compliance test methods for APIs, FPPs, starting/raw materials, intermediates and excipients.

1. The British Pharmacopoeia (BP);
2. International Pharmacopoeia (Ph.Int.);
3. United States Pharmacopoeia (USP);
4. Japanese Pharmacopoeia (JP);
5. European Pharmacopoeia (Ph.Eur.).

Whenever referenced, the specific edition and year of publishing must be stated.

In general Ph. Eur. does not include FPP monographs. Any references to the European pharmacopoeia must be clarified.

Each FPP should comply with the general requirements for dosage forms in pharmacopoeia.

Where a monograph exists in a pharmacopoeia, the vendor MUST follow the monograph methods.

In-house methods are considered acceptable where no official monograph exists in the acceptable pharmacopoeia listed above. Reference to “non acceptable” pharmacopoeia will be treated as in-house method.

Where an official acceptable monograph exists, the use of in-house methods is discouraged. If used, vendor MUST justify by giving an explanation AND providing a table comparing monograph and in-house methods side by side. As a general rule, it is expected that any in-house method/specification, should be tighter/more stringent than the official monographs in the acceptable Pharmacopoeia.

All in-house specifications and methods must be described in sufficient detail to enable all procedures to be repeated, including biological and microbiological analysis where relevant. The results of validation studies, including comments on the choice of routine tests and standards must be submitted as well.

SECTION 2 - ACTIVE PHARMACEUTICAL INGREDIENT(S), INTERMEDIATES AND EXCIPIENTS

APIs and excipients should comply with the current requirements of the acceptable Pharmacopoeia listed above. If not described in a pharmacopoeia, or manufacturer has additional specifications to those in the 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.

UNICEF requires FPP manufacturers to appropriately qualify their API suppliers (including site audits) and to submit a declaration confirming API supplier qualification. Site audit may be exempt for APIs that are WHO Prequalified or that have CEP or where API and/or intermediates manufacture site has been approved by WHO prequalification or Stringent Regulatory Authority (SRA). An API declaration form should be duly filled, signed and submitted together with the Interagency Finished Pharmaceutical Product Questionnaire and any time a new API source is introduced.

It should be possible to identify the all API manufacture processes and sites: manufacture of active substance by chemical synthesis, extraction of active substance from natural sources, manufacture of active substance using biological processes, intermediates. If necessary a flowchart should be provided to illustrate the role of all different sites involved.

In the case of introducing new API sources that are not supported by data already submitted, manufacturer should provide, as a minimum proof, that the new API can replace the old one. e.g. provide a table showing comparability of both methods of synthesis, particle size, etc. In addition, a minimum of 6 months accelerated stability data and 12 months long-term stability data for FPP with the new API source.is required. Less stability data with a commitment of ongoing stability data of FPP with new API source may be acceptable in certain circumstances.

In addition to API related documents submitted as part of the Interagency Finished Pharmaceutical Products Questionnaire, vendors must submit a UNICEF API declaration form, duly filled and signed by the FPP Qualified Person (QP)[2] with every solicitation and whenever API source changes.

SECTION 3 - FINISHED PHARMACEUTICAL PRODUCT

Manufacturing site(s) GMP status

The manufacturing site(s) including contract sites, where any aspect of manufacture occurs, must be stated. This includes production, sterilisation, packaging and quality control. UNICEF must approve all manufacture sites including contract sites and any changes in manufacturing site(s) at any time during the validity period of a Long Term Arrangement.

[2] A qualified person as defined by European Commission Directives OR Equivalent.

Both APIs and FPPs must be manufactured as per Good Manufacturing Practice (GMP) guidelines established by WHO.[3] [4] The vendor must submit a copy of the valid Manufacturing Licence and GMP certificates for the site where the API(s), intermediates and different types of FPP(s) and FPP dosage forms are manufactured, as issued by the relevant authorities in the country of manufacture/origin, stating the products and dosage forms authorised for manufacture at the respective site.

Vendors may be required to submit a copy of the most recent inspection report by the National Regulatory Authority or other agencies as listed in the IAFPPQ.

Contract manufacture

Vendor should state all details about contracting out part or all processes and relations to other companies, UNICEF must approve the site(s) of contract manufacture(s) and any changes thereof.

Inspection

Vendor(s) shall ensure that UNICEF or any other representative as may be designated by UNICEF, has access to all manufacturing facilities, including contract sites at all reasonable times. The vendor and/or manufacturer shall provide reasonable assistance to UNICEF or any other representative including providing copies of any documentation as may be necessary. The inspection may be carried out in conjunction with the relevant National Regulatory Authority.

General requirements for dosage forms

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 functional secondary/tertiary packaging strong enough to resist crushing and damage during transportation and storage;
5. Together with patient information leaflet or equivalent.

Method of manufacture and process validation

Submit a flow diagram and brief narrative describing the manufacturing control process of the FPP and provide a manufacturing method/process validation report (protocol if not yet validated).

It is very important to include batch size in the Certificate of Analysis (CoA) and stability reports and to give justification if it differs from the validated batch size.

In case of sterile products, data on validation on the sterile aspects of the product including media fill validation data and detailed description of method/s of sterilisation should be provided

Stability[5]

Supplier must demonstrate stability of the Finished Pharmaceutical Product throughout its intended shelf-life under the climatic conditions prevalent in UNICEF target countries. Majority of countries to which UNICEF supplies pharmaceutical products are in WHO climatic zones III, IVa and IVb.

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[3] 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>

[4] 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>

[5] World Health Organisation Technical Report Series (TRS) 953, 2009, Annex 2: Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. <http://www.who.int/medicines/publications/pharmprep/PDF_TRS953_WEB.pdf>

For the purpose of consistency and ease of logistics, UNICEF requires that all products supplied to or through UNICEF are suitable for transport and storage at Climatic zones IVb (30°C±2°C/75% RH ±5% RH) and with total shelf-life of 36 months or longer. Exceptions may apply only in situations where API/Active Moiety characteristics typically do not support zone IVb conditions and/or longer shelf-lives.

The FPP used for stability study should be the same as the FPP to be supplied to UNICEF with respect to product formula, all declared API sources, manufacture site and packaging materials. The vendor must declare which API sources have been used in the FPP under stability studies and commit to conduct stability studies for FPP using all declared API sources.

In the case of introducing new API sources that are not supported by data already submitted, manufacturer should provide, as a minimum proof, that the new API can replace the old one, e.g. provide a table showing comparability of both methods of synthesis, particle size etc. Less stability data with a commitment of ongoing stability data of FPP with new API source may be acceptable in certain circumstances.

1. Stability studies under the conditions defined for climatic zones IVb (30°C±2°C/75% RH ±5% RH) should be performed on each individual strength, dosage form and container type and size of the FPP unless bracketing or matrixing is applied. Reduced stability study designs such as bracketing and matrixing must be justified;
2. Stability testing should cover chemical, physical, biological and microbiological attributes, including preservative content. Tests should be conducted on those attributes that are susceptible to change during storage and transport and that can influence the safety, efficacy and quality of the product;
3. Stability studies, should be carried out on at least three primary[6] FPP batches and for every declared API source to be used in the FPP. As indicated in the WHO TRS 953 *"the primary batches should be of the same formulation and packaged in the same container-closure system as proposed for marketing. The manufacturing process used for primary batches should simulate that to be applied to full-scale production batches and should provide product of the same quality and meeting the same specification as that intended for marketing.";*
    a. *In the case of conventional dosage forms with APIs that are known to be stable, data from at least two primary batches should be provided;*
    b. *Two of the three batches should be at least pilot-scale[7] batches (pilot-scale should correspond to at least 10% of future/planned full-scale production batch size or 100,000 units, whichever is larger) and the third one can be smaller*. This is compulsory for FDC products and new APIs*, if justified;*
    c. Where possible, batches of the FPP should be manufactured using different batches of the API(s);
    d. Preference will be given to products with acceptable real time stability data from full-scale production batch sizes that cover the assigned shelf-life.
4. Results of six months accelerated stability studies and at least 12 months real time stability studies should be provided. Stability studies should be continued for a period of time sufficient to cover the entire shelf-life as allocated to the FPP;
5. The specifications and methods used during stability studies must be described in the stability protocol and report. 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. In general, specific methods, such as high-performance liquid chromatography (HPLC), thin layer chromatography (TLC) or gas chromatography (GC), must be used for the assay and determination of degradation products;
6. 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;
7. 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;

[6] Primary batch: A batch of a drug substance or drug product used in a formal stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf-life, respectively. A primary batch of a drug substance should be at least a pilot-scale batch. A primary batch may be a production batch.

[7] Pilot-scale batch: A batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For solid oral dosage forms, a pilot-scale is generally, at a minimum, one-tenth that of a full production-scale or 100,000 tablets or capsules, whichever is larger.

a. Each stability report should also include information about the type, size, and material of the pack, clearly stated stability conditions, FPP manufacture site address, API source(s) and batch size(s);
b. **IN-USE stability**: 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;
c. UNICEF takes note that some FPPs, e.g. those with marketing authorization in ICH regions may not necessarily be labelled for zone III and IV (non-ICH regions), even when supportive stability data exists;[8]
    i. UNICEF requires that products for supply to non-ICH zones be supported by stability data generated at 30°C±2°C/75%RH ± 5%RH (zone IVb) on the primary or production batches of the product in the same packaging as approved for marketing of the FPP by the reference regulatory authority/country/region;
    ii. If an FPP does not have zone IVb labelling, UNICEF requires that the vendor reviews stability data that the marketing authorization holder submitted for approval of the label storage conditions and shelf-life to the reference regulatory authority to determine suitability of supply to zone IVb climatic conditions. The vendor should submit to UNICEF the report of this review, along with the relevant stability data;
    iii. If zone IVb stability data is not available, the vendor should ensure that the manufacturer initiates full long-term stability testing at zone IVb conditions in the same packaging as approved by the reference regulatory authority. A minimum of 12 months long-term stability data is required. Considerations to accept product without acceptable zone IVb stability data and labelling will be on a case by case basis, driven largely by target country capacity to handle such a product.

Shelf-life and storage requirements

1. Shelf-life should be established based on complete long-term data at 30°C ±2°C/75% RH ±5% RH (zoneIVb). Total shelf-life of 36 months or longer is preferred.

2. The manufacture and expiry date that reflects the assigned shelf-life and recommended temperature storage conditions MUST be written on FPP labels and should be included in package inserts/patient information leaflets.
    a. Manufacture and expiry dates and the storage conditions must be consistent on the label, in the package inserts/patient information leaflets and throughout the submitted documentation;
    b. Statements such us "Store at room temperature" or "This product does not have special storage requirements" are not acceptable; The ACTUAL numerical temperature storage conditions MUST be specified.
3. In-use shelf-life: manufacturer MUST indicate storage conditions and shelf-life after reconstitution/dilution/opening, where applicable, such as powder for oral liquid, and powders for injection after reconstitution or injections that might be further diluted or multi dose containers such as ear/eye products.
4. Vendor is responsible to include additional labelling requirements such as "Do not freeze", "Protect from light", "Store and transport in dry conditions" on FPP and all external packaging.
5. UNICEF prefers fresh production to the extent possible. Total remaining shelf-life shall be reviewed at the time of procurement on a case by case basis.

Transport and transit storage requirements[9]

1. The vendor is responsible to SPECIFICALLY NOTIFY UNICEF about
    a. any special transport and storage requirements such as cold chain transport;
    b. any specific temperature requirements during transport and transit storage that are different from the conditions indicated on the product label.

[8] UNICEF recognizes that the requirement for zoneIVb labelling may result in a change to regulatory approved product information. For a limited time period, UNICEF may accept product with labelling other than zone IVb, together with acceptable stability data for zone IVb for the entire labelled shelf-life. This determination will be based on the ability of target countries to handle such product/information logistically, only if other products with zone IVb stability cannot be accessed at that time. It is therefore in the interest of the supplier to obtain the necessary regulatory approvals for change in labelled storage conditions and shelflife at the earliest opportunity

[9] http://www.who.int/medicines/areas/quality_safety/quality_assurance/ModelGuidanceForStorageTransportTRS961Annex9.pdf

2. The vendor MUST ensure that transport and transit storage temperature/humidity information and any other special handling conditions are clearly visible on documents accompanying the product during transport.

3. The transport and storage temperature and any other special handling conditions (e.g. DO NOT FREEZE) MUST be visibly indicated on external packaging such as shippers and pallets.
   The IATA Time and Temperature Sensitive Label (below) is a shipment label specific for the healthcare industry. It or an equivalent should be affixed to all shipments that are time and temperature sensitive (have a temperature requirement and shelf-life) indicating the external transportation temperature range of the shipment. IATA equivalent labels must also be affixed for products to be transported via other modes of transport such as sea/water and land.

4 The temperature indicated on the lower half of the IATA label or equivalent must match the approved transportation temperature range, e.g. +15ºC to +25ºC.

5 It is the responsibility of the vendor to inform the freight forwarder or any distributors accordingly and to ensure that product temperature conditions are maintained within acceptable limits during transport and transit. Regardless of the mode of transport, it should be possible to demonstrate that the product has not been exposed to conditions that may compromise their quality and integrity. A risk-based approach or delivery routes and modes of transport should be utilised when planning transportation.

Container-closure systems[10]

Container-closure systems is defined by UNICEF as the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection (e.g. light barrier) to the drug product.

Container-closure systems/packaging must preserve the stability and quality of the FPP during transport and storage for the duration of the shelf-life, including in-use shelf-life, where applicable. In some cases, child-resistant container-closure systems maybe required as an enhanced safety feature.

Vendors must demonstrate the suitability of the container-closure system used for the storage, transportation (shipping) and use of the FPP such as compatibility of the materials of construction with the dosage form, including sorption to container and leaching.

Container-closure systems must be tamper-evident i.e. it should be possible to know if the product has been altered or falsified.

[10] WHO Technical Report Series, No. 902, 2002, Annex 9: Guidelines on packaging for pharmaceutical products. http://apps.who.int/medicinedocs/documents/s19638en/s19638en.pdf

Primary Packaging[11]

1. Materials used for primary 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 FPP; 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 humidity[12];
2. The size of the container must be proportional to its content with the addition of appropriate padding to prevent damage to the product during shipment;
3. Glass containers will not be accepted above a maximum of 250 ml. Glass bottles must be separated by criss-cross box dividers or box partitions or be packed individually in cartons;
4. For glass ampoules, single ended, break-off necks are required. Non-glass packaging such as from "blow-fill-seal (BFS) technology (aseptic production of liquid injectables) are acceptable provided that all necessary compatibility and stability studies are adequate;
5. Primary packaging must bear appropriate labels providing content and usage information.

Dose measurement and dose delivery devices

1. A dose measurement and dose delivery device is required to be included with the container-closure system for administration of oral liquids or solids (e.g. solutions, emulsions, suspensions and powders or granules), whenever the package provides for multiple doses;
2. Dose measuring devices must be graduated in intervals to allow accurate measurement of all doses approved for that medicine;
3. The dosage scales/volumes embossed on dose measurement devices must be in METRIC units. The use of teaspoonful and other such measurements is not acceptable;
4. For oral liquids or powders for oral liquid, supplier is required to submit study results that confirm the suitability of the container-closure system contact materials and this should also include extraction studies and interaction studies (migration/sorption);
5. For a device accompanying a multi-dose container, the results of a study should be provided demonstrating the reproducibility of the device (e.g. consistent delivery of the intended volume). A description of the container-closure systems should also be provided, including the identity of materials of construction of each primary packaging component (including those used for drug delivery) and its specification;
6. An applicator is required to be included with vaginal pessaries.

Secondary packaging[13]

A pack component normally not in direct contact with the product.

UNICEF accepts secondary packaging that is functional i.e. adds protection to that provided by the immediate primary pack against

1. Excessive moisture and reactive gases, e.g., fibre drums, HDPE bottles for products which are immediately packaged with LDPE bag;
2. Light, e.g. carton outside PVC/Alu blister;
3. Microbial and dirt contamination;
4. Rough handling during transport and storage.

Secondary packaging may also be acceptable if they provide a means to contain summary of product characteristics/patient information leaflets and/or dosing devices.

Information related to the functionality of the secondary packaging must be provided in the dossier submission.

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[11] this refers to placing and sealing of the medicinal product within the finished product packaging material which is in direct contact with the product.

[12] 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>

[13] this refers to placing the medicinal product, which is already sealed within its primary packaging material within an outer packaging material. This also includes labelling operations or the assembly of other components which are specified in the Marketing Authorisation to form the finished product pack.

Commercial/marketing pack
A combination of primary and secondary packaging, whether or not the latter has any overt stability maintenance function.

Packaging to improve Supply Logistics efficiency and for sustainability
In addition to protecting FPP and providing information to support FPP usage, packaging should:

1. Improve supply logistics and operational efficiency at minimal costs;
2. Ensure user-friendliness and support patient compliance;
3. Maintain safety and minimize medication errors;
4. Be tamper-proof and/or tamper-evident;
5. Make product handling easier, efficient and more automated by use of standard smart barcodes e.g. EAN 13, UPC or Code 39 placed in a manner that it can easily be read. Other smart codes such as QR codes are acceptable;
6. Enable traceability and supply chain safety e.g. incorporate Track-and-Trace systems that assure chain of custody and/or anti-counterfeiting measures;
7. In line with sustainable procurement efforts, vendors are asked to consider to eliminate non-functional secondary/tertiary packaging WITHOUT compromising the integrity of the FPP and while still ensuring that sufficient product information to health professionals and patient is available together with the product.

Labels

Labels must be self-adhesive and made from paper, e.g. pharmaceutical defiberised paper (80gsm), that is film or UV coated for protection against humidity and firmly affixed to be tamper proof and to prevent detachment in tropical climates.

Language	English and/or French is the standard language for labels and pack inserts. Arabic, Portuguese, Russian and Spanish may be requested from time to time. Other local languages specific to recipient country may be requested with specific tenders and/or purchase orders.
Type	Preferably by lithography directly on container/packaging.
Ink/colour	The writing on primary and secondary packs must be in indelible ink, preferably in black on white.

Information required on labels
Labels must have adequate information to permit identification, safe transport, storage and use of the product throughout its shelf-life. In certain instances, labelling and patient information in Braille or AUDIO may be required.
At the minimum, the FPP label must contain

1. Name of the medicine; The International Non-proprietary Name (INN) name, pharmaceutical form and strength should be written in a bold, clearly visible, large font size. For large volume parenterals, the INN name of the medicine should be readable in both the upright and upside down (inverted) positions
    a. If an International Non-proprietary Name (INN) (also referred to as the generic name) recommended by the World Health Organisation exists for the active moiety, the English version of the name should be used exactly as published without omissions or abbreviations;
    b. If a Modified INN (INNM) recommended by the World Health Organisation has been published for the active moiety, it should be used within the name of the medicinal product exactly as published without omissions or abbreviations;
    c. Where the active moiety is an unpublished INNM, the name of the medicinal product should be that as agreed by users of INNs (Pharmacopoeias, regulatory bodies, stakeholders), in accordance with the WHO INNM working document 05.167/3;
    d. If an INN or INNM does not exist, other common names, such as the British Approved Name (BAN) are acceptable. Information on INN names and stems is available from WHO http://www.who.int/medicines/services/inn/en/
    e. The expression of the amount or percentage of API or active moiety per dosage unit, unit of volume or unit of weight should be in metric units.
2. Names and amounts of excipients of medical and/or pharmaceutical relevance, e.g. “contains 10% ethanol”, “contains lactose”. If the pharmaceutical product is a parenteral, topical, inhalational or an eye preparation, all excipients must be stated;
3. Pharmaceutical dosage form;
4. Route of administration;
5. The pharmacopoeial reference used for the FPP, where applicable. Pharmacopoeia reference should only be included in the name of the product where ALL standards and analytical methods for the product refer

to that pharmacopeia. It should not be used where in-house standards and methods are used or where more than one pharmacopoeia reference is used;
6. Net quantity per unit pack labelled on that unit pack (primary, secondary, tertiary) in metric units in a visible manner;
7. Posology and directions for use for the target group(s);
8. Any special instructions for use e.g. “to be swallowed whole - do not chew”;
9. Recommended temperature requirements during transport and storage;
10. Special storage and handling instructions, including warnings and precautions;
11. If a product has a limited shelf-life after the primary package is opened and manipulated, the in-use period and storage condition should be indicated on the label;
12. Batch identification;
13. Manufacture date in a format that can be easily understood. The recommended format is DD/MM/YYYY. To avoid confusion, the year of manufacture should be 4 digits;
14. 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;
15. Name and address of manufacturer and marketing authorisation holder. For contract manufacture, indicate as: manufactured by company X for company Y.

Best practices on label formats and style (non-binding requirements)

1. Information 1-7 listed above should appear clearly on the front face of the label AND in the same field of view, without any additional information or logos or background texts or graphics;
2. The strength of the API (or active moiety) should at all times appear next to the name of the API (or active moiety), e.g. Artemether 20mg + Lumefantrine 120mg;
3. Components in fixed dose combination FPPs (FDCs) and co-packs 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;
   Where another names such as British Approved Names is used, e.g. Co-Amoxiclav the INN names of the two active moieties should be stated with their full INN names i.e. Amoxicillin 500mg + Clavulanic Acid 125mg;
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, pack inserts/patient information leaflets [14]

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

It is MANDATORY to include a package insert and/or patient information leaflet with each FPP either within the secondary packaging or as part of the label or attached on top of the package. *Additionally, electronic means of providing information, such as QR codes are encouraged*

Safety, efficacy and/or therapeutic equivalence

The report of the proof of therapeutic equivalence (bio-equivalence or multimedia comparative in vitro dissolution profiles or any other method), should be submitted as outlined in the Interagency Finished Pharmaceutical Product Questionnaire or its equivalent.

[14] See the WHO prequalification programme (PQP) ‘Guidance on Patient Information Leaflet, Summary of Product Characteristics and Labelling. http://apps.who.int/prequal/

The product used in the therapeutic equivalence study should essentially be the same as the one that will be supplied i.e. same materials from the same suppliers, same formula and same manufacturing method(s).

Submission of such a report of proof of therapeutic equivalence may not be required for FPPs that are WHO prequalified or approved by an SRA that requires proof of therapeutic equivalence to be submitted as part of their dossier evaluations for marketing authorization/product registration.

For innovator products, a summary report of pharmacology, toxicology and efficacy of the product should be submitted.

Certificates of Analysis

A Certificate of Analysis is issued following full qualitative and quantitative analysis of all relevant aspects of the product and in compliance with its marketing authorization.

For all FPPs, certified copies of certificates of analysis as per WHO Model Certificate of Analysis format (WHO Technical Report Series, No. 902, or latest version) for the last three production batches are required for submission with tenders.

Certificates of analysis must also accompany products when they are delivered to UNICEF or designated UNICEF consignees.

Where applicable this batch specific CoA may be required for non-finished medicinal products such as intermediates, bulk or partially packed products.

The CoA should state the specifications tested, the results and the conclusion of the testing
The CoA should be numbered in such a way that it is possible to identify the current page and the total number of pages in the CoA e.g. page x of y.

For all CoA quantitative specifications, numerical values of results must be stated. The word “complies” or “conforms” is NOT acceptable in place of numerical values.

Suitability of invented/brand names or registered trade names

UNICEF prefers that ONLY the International Non-proprietary Name (INN) is written on all labels and pack inserts. Where proprietary, brand or registered trade names are used, the International Non-proprietary Name (INN) must be more prominent e.g. in bigger font than the proprietary, brand or registered trade name.

In accordance with World Health Assembly (WHA) resolution 46.19, an invented/brand name should not be derived from its own INN or INN stem. If used, the invented/brand name, strength and pharmaceutical form

1. Should be the same as that registered in the summary of product characteristics (SmPC);
2. Should not cause confusion with the INN name of this medicine or name of another medicine in print, handwriting or pronounciation;
3. Should not be misleading with respect to therapeutic effect, composition or safety of the product. Words in the brand name such as “forte”, “strong”, “fast-acting”, “extra”, “double strength”, should not be used UNLESS supported by evidence/data in the SmPC and relevant to the indications approved for the product;
4. Must not be so prominent as to mask the appearance and readability of the INN.

Sustainable procurement

1. In line with sustainable procurement efforts and to eliminate waste, vendors are asked to consider to eliminate non-functional secondary/tertiary packaging WITHOUT compromising the integrity of the FPP and while still ensuring that sufficient product information to health professionals and patients is available together with the product;
2. Where necessary, vendors should use sustainable packaging against sustainability standards;
3. Vendors should consider the lifecycle of the product and provide evidence to that effect.

Notification of changes

UNICEF should be notified and approve of any changes in the API and/or Finished Pharmaceutical Product specifications or changes to any of the aspects that have been technically evaluated and approved.

SECTION 4 - HOW TO SUBMIT PRODUCT DOSSIERS

This section is intended to ensure that product dossiers are submitted in a manner that they can be easily identified, stored, retrieved and assessed in an efficient manner.

The content of this section should be read in conjunction with the Interagency Finished Pharmaceutical Product Questionnaire (IAFPPQ). The full name of the Annex document must be in the title of the document e.g. *Annex A. Formulation of the product* http://www.unicef.org/supply/files/InteragencyFisnishedPharmaceuticalProductquestionnaire_doc.pdf

1. Documents should be submitted in suitable electronic formats, as indicated with each solicitation or contractual modality. **Physical paper files are no longer acceptable for technical documents.** Each **electronic dossier** must have the following information
    a. The solicitation or contractual document reference number e.g. RFP-DAN-XXXXXX or PO 45XXXXXX;
    b. Vendor and/or manufacturer name and contact details;
    c. The words “DOCUMENTS FOR TECHNICAL ASSESSMENT”;
    d. Table of contents so as to enable easy location of the relevant documents in the electronic file;
    e. All documents should be submitted in the same sequence as listed in section 6 of the IAFPPQ;
    f. A cover letter confirming that all the information submitted is complete and correct. Any exceptions must be highlighted in the letter;
    g. The full name of any annex as stated in section 6 of the IAFFPQ clearly written as part of the title of the document e.g. Annex A. Formulation of the product.
2. 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;
3. All documents submitted must be typed in readable font type and size in black on white, duly signed and submitted in pdf format. No handwritten documents will be accepted
   Font type: Verdana preferred
   Font size: Minimum 10, Maximum 14
4. All documents/filled forms shall have no interlineations, erasures, or overwriting. Any necessary corrections shall be initialled by the person or persons signing the bid;
5. Vendors should also complete and submit electronically the UNICEF Technical Questionnaire for Pharmaceutical Manufacturers https://www.unicef.org/supply/index_52844.html

Documents to be submitted

a. All documents must be submitted as requested and listed in Section 6 of the Interagency Finished Pharmaceutical Product Questionnaire (IAFPPQ) http://www.unicef.org/supply/index_52844.html
b. Submit a separate complete electronic file for each FPP. An FPP is considered a separate product if it has its own Certificate of Pharmaceutical Product (CoPP/CPP);
c. The annexes to the Interagency Finished Pharmaceutical Product Questionnaire should not be merged into a single pdf document. Please ensure that each of the annexes are saved as separate pdf files. This will simplify navigation through the submission and facilitate the dossier review. See below as an example;

Annex-A - Batch Formula
Annex-AA - Graphic summary of BE results
Annex-AB - BE Study Report
Annex-B - Primary Packaging
Annex-C - Secondary Packaging
Annex-D- Manufacturing licence
Annex-E-CPP
Annex-G-WHO prequalification letter
Annex-I-Labeling
Annex-J- SmPC and PIL
Annex-K - API GMP certificate
Annex-L - API specification
Annex-M - Method validation
Annex-O - API COA
Annex-P1 - CEP certificate
Annex-P2 - Technical File
Annex-Q - FPP GMP certificate
Annex-R - FPP Specifications
Annex-S - FPP COA
Annex-T - Process Flow Sheet
Annex-V - Stability Data
Annex-W - Stability Declaration
Annex-X - Status of On-going Stability
Interagency Finished Pharmaceutical Product questionnaire
Other doccuments - API Declaration form
Other documents - Indicate name of document here
Signed pages

d. The bidder is responsible to ensure that any documents not requested or not listed in section 6 of the IAFPPQ, but may be required or would add value to the technical evaluation are submitted as an additional file e.g. vendors must submit an API declaration form, duly filled and signed by QP as part of any solicitation process or when API sources change.

SECTION 5 - HOW TO SUBMIT PRODUCT SAMPLES

Vendors may be required to submit a specified number of non-returnable samples to enable visual and organoleptic examination. Such samples should be in their final status and packaging as intended to be supplied on purchase orders, including pack inserts and dose measuring devices (here in after referred to as commercial/market sample). Commercial/market samples will normally be accepted up to one week after the solicitation closes. Please do not submit more samples than requested.

In cases where samples submitted are NOT commercial samples, they MUST be labelled as NON-COMMERCIAL SAMPLE. A justification why a commercial sample cannot be submitted must be included with the submitted sample.

The information below serves as a guide and as the minimum requirements. Vendor should pay specific attention to the actual requirements in each solicitation activity.

1. For solid oral dosage forms with several pack sizes:
   - Submit the lowest pack size as sa complete and intact sample for each packaging type e.g. HDPE bottle, blister packs;
   - Submit subsequent pack sizes of each packaging type within the correct primary and secondary packaging, including package insert with the full number of dosage units in this pack size OR the same number of dosage units as that of 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 a minimum of two (2) bottles/packs;
4. Exceptions may apply for example, for controlled medicines, UNICEF may accept FPP packaging and package insert/patient information leaflet without the medicine.

NOTE: UNICEF Supply Division[15] regularly requests and receives samples from a variety of vendors. It is VERY IMPORTANT for the vendor 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.

SECTION 6 – COMMITMENT

Vendors must fulfil commitments they have made at any time and report back to UNICEF e.g. carrying through stability studies, validation of batch sizes.

Vendors must fill, duly sign and submit the UNICEF commitment declaration form where required.

For all products on LTA or contract with UNICEF, vendors shall inform UNICEF immediately about

1. Any serious quality and/or safety concerns about their manufacture, control or use;
2. Suspension or cancellation of marketing authorisations;
3. Suspicion and/or confirmation of falsification.

The vendor pledges to work with UNICEF to minimise potential public health risks by actively organizing product recalls of defective products and either 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.

[15] http://www.unicef.org/supply/index.html