Technical Requirements for Micronutrient Products

Version No.: 1 (first edition)
Issue Date: 27.02.2026

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Abbreviations & Acronyms

CoA: Certificate of Analysis

CoPP: Certificate of Pharmaceutical Product. Also referred to as CPP

FSC: Free Sales Certificate or Certificate of Free Sales

ICH: International Council for Harmonization of Technical Requirements for Pharmaceuticals for human use.

IAFPPQ: Inter-Agency Finished Pharmaceutical Product Questionnaire

JECFA: Joint FAO/WHO Expert Committee on Food Additives

LTA: Long-Term Agreement

MQAS: WHO's Model Quality Assurance Scheme

NRA: National Regulatory Authority

PO: Purchase Order

RFP: Request for Proposal

RFQ: Request for Quotation

SO: Sales Order

SRA: Stringent Regulatory Authority

TQPM: Technical Questionnaire for Pharmaceutical Manufacturers

UNGM: United Nations General Market

WHO PQ: World Health Organization Prequalification

WHO: World Health Organization

WLA: WHO Listed Authority

GLOSSARY

Active Ingredient: Active ingredient refers to the active moiety that provides pharmacological activity in the case of an Active Pharmaceutical Ingredient (API), or nutritional or physiological activity in the case of nutritional ingredients.

Active Pharmaceutical Ingredient (or Active Ingredient): Any substance or mixture of substances used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substance is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Competent Authority: A competent authority is an officially designated government body with the legal mandate, authority, and technical capacity to regulate, supervise, inspect, and enforce compliance within a defined regulatory scope, with varying responsibilities for product authorization, manufacturing oversight, inspection, certification, and/or enforcement under national legislation.

Dosage form: The physical form of a finished product in which an active ingredient is made available in a particular formulation and presentation, intended for administration to a patient (e.g. tablet, capsule, oral liquid, injection, topical cream).

Drug product: A drug product is a substance or a pharmaceutical product that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient. In this document, the terms drug, and pharmaceutical are used interchangeably. For simplification, the word 'product' is mostly used.

Essential Medicine List (EML): The National Essential Medicines List (EML) identifies medicines that meet the priority health needs of populations, selected for their public health relevance, proven efficacy, safety, and cost-effectiveness. Updated every two years, the WHO Model List of Essential Medicines serves as a guide for countries to develop or revise their own national essential medicines lists, ensuring availability of quality-assured medicines in appropriate forms at affordable prices for individuals and health systems.

Excipient: is an ingredient other than the active substance, added in the formulation for a specific purpose. While most excipients are considered inactive, some can have a known action or effect in certain circumstances.

Finished product: A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labelling. In this document, the terms finished product and product are used interchangeably.

Good Manufacturing practice (GMP): is a system for ensuring that the products are consistently produced and controlled to quality standards in line with its intended use.

Good Storage/Distribution Practices: refers to the part of quality assurance that ensures that the quality of medical products is maintained by means of adequate control throughout the storage thereof and throughout the numerous activities which occur during the distribution process.

Inter-Agency Finished Pharmaceutical Product Questionnaire (IAFPPQ)[1]: A standardized questionnaire used by international procurement agencies (e.g. UNICEF, MSF, WHO, ICRC) to collect detailed information on a finished product including its formulation, manufacturing site(s), active ingredient(s), packaging, stability, regulatory status and quality documentation — to support technical assessment and quality assurance of the product.

Intermediate product: Partly processed product that must undergo further manufacturing steps before it becomes a finished product.

Marketing Authorization Holder: A corporate body which holds an authorization to place a pharmaceutical product in the local market and is responsible for that product.

Marketing Authorization (Product license or Registration Certificate): A legal document issued by the competent medicines regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labelling and shelf-life.

National Medicines Regulatory Authority (NMRA): The official regulatory authority of a country designated to administer regulatory activities related to Medicines. This term is used interchangeably throughout the document with NRA i.e. National Regulatory Authority.

Nutritional Ingredient: is a vitamin, mineral, amino acid, or other substance with nutritional or physiological effect on the structure and function of the body, intended to supplement the diet. In this document, the term Active Ingredient is used interchangeably with Nutritional Ingredient.

Pharmaceutical Inspection Cooperation (PIC/S): An international arrangement between regulatory authorities that aims to harmonize Good Manufacturing Practice (GMP) standards and inspection procedures worldwide, promote mutual confidence among inspectors, and facilitate mutual recognition of GMP compliance.

Pharmaceutical product: Any material or product presented in its finished dosage form, or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state. In this document, the terms drug product and pharmaceutical product are used interchangeably. For simplification, the word 'product' is mostly used.

[1] https://www.unicef.org/supply/documents/interagency-finished-pharmaceutical-product-questionnaire

Pharmacopeial Standard(s): is defined as a set of guidelines and specifications that govern the identity, purity, strength, and quality of pharmaceutical products and their ingredients.

Pilot-scale batch: A batch of the product manufactured by a process fully representative of and simulating a full production-scale batch. For example, 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.

Production (or Commercial batch): A batch of an ingredient or finished product manufactured at production scale by using production equipment in a production facility as specified in the application. In this document, the term production match is used interchangeably with commercial batch.

Specification: A documented set of quality standards to which a product should conform to be considered acceptable. It normally includes detailed information on product composition, a list of required quality attributes and associated analytical tests and procedures, with references to pharmacopeial or in-house standards, and appropriate acceptance criteria.

Stringent Regulatory Authority (SRA): refers to a regulatory authority which was, prior to 23 October 2015:

(a) a member of the ICH; or

(b) an ICH Observer, being the European Free Trade Association (EFTA) as represented by Swiss Medic and Health Canada; or

(c) a regulatory authority associated with an ICH member through a legally binding mutual recognition agreement including Australia, Norway, Iceland and Liechtenstein (as may be updated from time to time).

Technical Questionnaire for Pharmaceutical Manufacturers (TQPM[2]): A questionnaire to be completed by pharmaceutical manufacturing sites (or contract manufacturers) responding to a solicitation process to supply products to agencies, gathering information on the manufacturer's site, personnel, quality systems (GMP/GDP), production capacity, product licenses, and manufacturing operations — used to assess manufacturer capability, risk, and need for inspection or audit.

Variation: A change to any aspect of the finished product, including but not limited to, the change of use of a starting material, a change to formulation, method and site of manufacture, specifications for the finished product and ingredients, packaging and labelling and product information.

WHO Listed Authority (WLA): refer to a regulatory authority or a Regional regulatory system which has been listed by WHO to comply with all the relevant Global Benchmarking tool

[2] https://www.unicef.org/supply/documents/technical-questionnaire-pharmaceutical-manufacturers

indicators and performance requirements specified by WHO for the requested scope of listing based on an established benchmarking and performance evaluation process.

WHO normative standards and guidelines: Evidence-based technical documents developed through expert consultation to guide Member States in health policy and regulatory practices, e.g. the *WHO Technical Report Series (TRS)* and related normative publications on quality, safety, and efficacy.

WHO Prequalification (WHO PQ): A WHO-managed programme that prequalifies medicines, vaccines, diagnostics, and quality control laboratories found to meet global standards of quality, safety, and efficacy for UN and partner procurement.

BACKGROUND

UNICEF aims to ensure timely and affordable access to safe, effective, quality medicines and nutrition products in both development and humanitarian contexts. UNICEF's product portfolio is designed to meet global demand while also addressing specific needs of countries and partners. The UNICEF Supply Catalogue lists the standard range of products available for routine procurement, while additional non-standard products may be sourced on behalf of governments, UN agencies, non-governmental organizations, philanthropic foundations, and academic institutions.

UNICEF procures and supplies Micronutrient Products in line with UNICEF's Technical Requirements, Good Manufacturing Practices (GMP), supply chain controls, and applicable regulatory oversight to ensure quality and safety risks are managed throughout the product life cycle. Only products and manufacturers that have undergone a full quality assessment, including technical dossier review and GMP inspection, and are found acceptable by UNICEF or other recognized entities, are eligible for procurement.

The Technical Requirements for Micronutrient Products outlines UNICEF's expectations regarding quality and safety of the products and manufacturer's GMP. The document serves as a guidance for suppliers, when responding to a UNICEF solicitation[3].

When responding to a solicitation activity, suppliers (manufacturers, distributors, wholesalers) are required to fill in and submit the following technical questionnaires:

1. The Inter-Agency Finished Pharmaceutical Product Questionnaire (IAFPPQ), which is focused on product quality information
2. Technical Questionnaire for Pharmaceutical Manufacturers (TQPM), which is focused on facility and operational GMP information

The products covered by this Technical Requirements document are listed in Annex I of this document.

The Technical Requirements document must be read in conjunction with the Product Specification(s) as elaborated in each solicitation activity. Together with the product specification, the requirements outlined in this document form a critical component of the contractual framework applied to LTAs and PO(s).

For clear comprehension of the expected compliance with the requirements laid in this document, the following verbal forms are used:

- "must" indicates a requirement
- "should" indicates a recommendation

[3] Procurement processes, as launched on United Nations General Marketplace, such as Invitations to Bid (ITBs), Requests for Quotations (RFQs), or Requests for Proposals (RFPs) potentially leading to i.e. Long-Term Agreement (LTA) and Purchase Order (PO).

- “can” or “may” indicates a possibility

Note: References to WHO Technical Report Series (TRS) documents or guidelines from the International Council for Harmonization (ICH) are to the latest available version.

Additional Note: This Technical Requirements document does not cover products where the route of administration is parenteral.

1. General requirements

This section covers general information regarding the product's identification, regulatory compliance requirements, and analytical testing standards.

1.1. Product Identification

The following requirements concern section 1.1 of the IAFPPQ.

1. Finished Product or Product should be identified by its International Non-proprietary Name(s) (INN). Generic name(s), British Approved Name(s) (BAN) or others such as pharmacopeial monograph title for the product should be stated if different from INN. UNICEF does not recommend the use of trade (proprietary) names and does not approve the same.

2. The Active Ingredient(s) should be identified by its (their) INN, along with its(their) pharmacopeial monograph reference and chemical form such as base, salt, or ester compound.

3. Dosage form: The dosage form and dosage form attributes must be specified e.g., if tablets are functionally scored, dispersible, enteric coated, bi-layered, film coated, sugar coated, what release mechanism the product has (immediate or modified); or whether the formulation is presented as oral drops, oral solution, or oral suspensions.

4. Strength of each active ingredient per dosage unit or the amount of active ingredient(s) per dosage unit should be provided. Where this is specified in terms of salt, or ester, the equivalent amount of active ingredient must be specified. E.g. formulations in which the strength is expressed in terms of the active ingredient, with the corresponding salt indicated in parentheses — *e.g.* "65 mg iron (as ferrous sulphate)" or "36 mg iron (as ferrous fumarate)". For further guidance on indicating strength of active ingredient(s) refer to:

    - *WHO Technical Report Series, No. 957, WHO Expert committee on specifications for pharmaceutical preparations, chapter 11. Miscellaneous, page 62*

5. Batch formula: The complete product master batch formula including chemical forms of all active ingredients and excipients should be submitted. Overage used in the formulation must be reported. The batch formula must specify use of any premixes. The batch formula must be submitted in *Annex A* of the IAFPPQ.

6. Product format: Whether a product is a fixed-dose combination (FDC) or co-pack or co-formulated (as two or more components in fixed proportions in a single dosage form) must be specified.

1.2. Regulatory Compliance

The following requirements concern section 1.6 of the IAFPPQ and supporting documents must be submitted in *Annex D* and *E*.

1. Product registration: Documentation proving that the finished product is registered/licensed in the country of manufacture/origin, as per all applicable national regulations must be submitted.
2. Type of product registration: Whether the product is marketed in that country or registered for EXPORT ONLY must be indicated.
3. Drug Manufacturing license number: UNICEF prefers that the active ingredients and finished product(s) covered by this document is(are) manufactured at a site(s) holding Drug manufacturing license(s), with demonstrated application of WHO Good Manufacturing Practices, certified by the National Regulatory Authority.
4. Drug Selling License: (if the supplier is different from the manufacturer) a copy of their valid Wholesale and/or Distribution license.
5. Product registration in other countries: if the product is registered in other countries, the issuing NRA, and the respective licenses or registration numbers and validity periods must be provided. Registration in countries where UNICEF supplies the finished product is recommended.
6. Certificate of Pharmaceutical Product (CoPP or CPP) for the Product issued by the National Regulatory Authority in the country of manufacture/origin, should be provided. The certificate format should be as per:
    - *WHO Technical Series No. 1033 Annex 9: Guidelines for implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce*.

    If a CoPP cannot be obtained, state the reason. In such cases, a Free Sales Certificate (FSC), or equivalent, issued by the competent NRA, must be provided.

1.3. Pharmacopeial Standards

The following requirements concern sections 2 and 3 of the IAFPPQ.

UNICEF recognizes the following pharmacopoeias for active ingredient(s), excipients, and finished product(s) monographs. Whenever referenced, the specific edition and year of publishing must be stated.

1. British Pharmacopoeia (BP)
2. European Pharmacopoeia (Ph. Eur.)

3. International Pharmacopoeia (Ph. Int.)
4. United States Pharmacopoeia (USP)
5. Japanese Pharmacopoeia (JP)

Conformance to pharmacopeial standards is determined by the official tests, procedures, and acceptance criteria and other requirements incorporated in the monograph and applicable general chapters.

Note: Pharmacopoeia other than the ones mentioned above (e.g. Indian Pharmacopeia) will be treated as in-house standard.

1.4. Analytical Testing

The following requirements concern section 2.1 and 3.2 of the IAFPPQ and supporting documents must be submitted in *Annex M* and *T*.

1. When an official pharmacopeial monograph exists for active ingredient(s), finished product(s) and/or excipients, test methods as elaborated in the monograph must be followed. Manufacturers must verify the suitability of the Pharmacopeial monograph methods under actual conditions of use and the results of verification studies must be submitted.
2. When using an official pharmacopeial monograph, with an in-house modification, the methods must have been validated.
    - A tabular comparison of the reference pharmacopeial method and in-house modified method (highlighting the modification), with an adjacent column detailing justification for the modifications.
3. In-house methods are acceptable only when no pharmacopeial monograph method exists or are demonstrated to be equivalent to pharmacopeial standards. When using in-house specification/methods, the following must be submitted.
    - Detailed in-house method(s).
    - In-house analytical methods validation protocol and the report, including demonstration of equivalency when equivalency to pharmacopeial method is claimed.
4. In certain cases (e.g., dissolution method and limits), product-specific in-house methods may be acceptable even when an official monograph exists. Where applicable, specific dissolution requirements are outlined in UNICEF's product specification.

Reduced testing for active ingredients: UNICEF may consider reduced testing plans as part of a manufacturer's ingredient control strategy, provided they are supported by a comprehensive Quality Risk Management (QRM) framework. Acceptance of such plans requires that:

- ingredient suppliers have been qualified through a rigorous and ongoing supplier approval program;
- the reliability of supplier CoA results is demonstrated initially and periodically;

- the manufacturing process is validated and statistically controlled; and
- statistically sound sampling and testing plans are established and maintained.

Reduced testing for finished product: For complex, multi-component formulations such as United Nations International Multiple Micronutrient Antenatal Preparation – Multiple Micronutrient Supplement (UNIMMAP MMS), reduced testing is not accepted during initial evaluation but may be adopted later upon consistent demonstration—across multiple commercial batch production of the finished product—for process accuracy, reproducibility, quality assurance and control. A reduced testing program should include rotational testing (e.g., representative oil-soluble vitamin, water-soluble vitamin, and mineral tested at statistically relevant frequency sufficient to ensure representativeness of routine production.

Implementation must be supported by:

1. A documented risk assessment and verification plan, including clear criteria for reverting to full testing;
2. Evidence of a robust supplier qualification program with sustained compliance of all raw materials;
3. Evidence that the manufacturing process has been validated; and
4. Trend analysis and acceptable process capability studies confirming manufacturing process consistency.

Guidance on implementation of Quality Risk Management principles can be found in the following references:

- *WHO Technical Resource Series, 981 - Annex 2: WHO guidelines on quality risk management*
- *ICH Q9(R1) Quality Risk Management*

1.5. Certificate of Analysis

The Certificate of Analysis (CoA) should be as per:

- *WHO Technical Report Series, 1010 – Annex 4: Model certificate of analysis*.

The CoA must be dated and clearly indicate:

1. Manufacturer and laboratory details: Name and address of the manufacturing and testing sites.
2. Specifications and results: Applied test limits and corresponding analytical results for each active ingredient.
3. Batch information: Batch number, batch size, manufacture and expiry dates.
4. Pack details: Pack size and packaging format.
5. Conclusion: Statement of compliance with product specifications.

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

Theoretical test results are not acceptable. If tests are not performed, it should be justified and there should be a footnote in the CoA explaining whether this is as per reduced testing plans, where such an approach has been agreed with UNICEF.

2. Active Ingredients, Intermediates and Excipients

Manufacturers are recommended to undertake thorough comparability and compatibility studies during initial product development stage to develop a deep understanding of the nature of the ingredients. Special attention must be paid to potential interactions, sensitivity and stability issues.

Compatibility studies must be conducted to ensure no interactions occur between the ingredients that could affect the physical, chemical, or safety characteristics of the product. Impurities and residual solvents (including organic impurities, reagents, and catalysts) must be assessed and controlled to ensure product safety and efficacy.

Special attention should be given to ingredients containing raw materials of animal origin (e.g. gelatine). The use of such materials should be avoided where possible. Where their use is unavoidable, a valid BSE-Free Certificate (Bovine Spongiform Encephalopathy) should be available and provided upon request. The certificate must confirm the absence of prohibited materials, including specified risk materials or other ruminant-derived tissues, and demonstrate that sourcing, manufacturing, and packaging processes are free from BSE contamination.

When sourcing ingredients or intermediates, e.g., Vitamin and/or Mineral premixes, manufacturers must source from ingredient manufacturers that demonstrate compliance to Good Manufacturing Practices as per:

- *WHO Technical Report Series, 957 – Annex 2: good manufacturing practices for active pharmaceutical ingredients (bulk drug substances)*
- *WHO Technical Report Series, 885 – Annex 5: good manufacturing practices: supplementary guidelines for the manufacture of pharmaceutical excipients*

2.1. Details of Active ingredients

The following requirements concern sections 2.1, 2.2, 2.4, and 2.5 of the IAFPPQ.

1. Active Ingredient specification(s): must include the chemical form (INN), reference monograph, composition, assay and purity, physical and chemical characteristics, country of origin, religious or dietary certifications, stability and storage and handling.
   Active Ingredient specification(s) from the finished product manufacturer must be submitted in *Annex L*.

2. Analytical testing validation data: If analytical methods are in-house, the detailed method and the validation report must be submitted as *Annex M*. Please refer to section 1.3 of this document for additional guidance.

3. Manufacturing site(s) and processes: All manufacturing sites involved in the production of the active ingredient must be listed, and each stage of the process—from starting materials to the final active substance (e.g., biological production, extraction, purification, and intermediates) —must be described. Where necessary, a flow-chart should be provided to illustrate the role of the different manufacturing sites involved. Furthermore, when using different sources of active ingredients, detailed manufacturing process for each source should be submitted, as part of demonstrating comparability, in *Annex R*.

4. GMP compliance and certification: Last GMP audit conducted by SRA, NRA, PIC/S or other competent authorities must be indicated and the cGMP certificate issued by the SRA/NRA must be submitted as *Annex K* of the *IAFPPQ*.

   Exceptionally, GMP certificate issued by an accredited third-party auditor or auditing body may be considered, subject to strong justification as to why a GMP certificate from an SRA, NRA, or other competent authority cannot be provided. Additionally, in such cases it is recommended that finished product manufacturer conducts comprehensive on-site audit(s) in accordance with their own documented supplier-evaluation procedure.

5. Certificates of Analysis (CoA): A copy of the most recent CoA from the active ingredient manufacturer as well as the product manufacturer must be submitted in *Annex Q* of the IAFPPQ. The CoA must clearly indicate the laboratory address and accreditation.

Additionally, the following requirements may be checked and supporting documentation may be requested.

1. Active Ingredient supplier qualification process: While this is checked in detail during the UNICEF GMP inspection, UNICEF may want to understand the Product manufacturers qualification program for their ingredient suppliers at Technical Dossier evaluation stage or as part of preparation for the GMP inspection. When requested, the manufacturer must provide a summary report of how each ingredient manufacturer was qualified, including the outcome, date of last audit and by whom the activities were performed. Audit reports as issued to the ingredient supplier may be requested.

2. Material Safety Data Sheet (MSDS)

3. Open part of the Drug Master File (DMF) or CEP (Certification of Suitability to the Monographs of the European Pharmacopoeia), if available, for the active ingredient registered in the country of origin.

2.2. Details of Excipients

The following requirements concern sections 1.2 of the IAFPPQ and though not specified in the IAFPPQ, the below mentioned supporting documents must be submitted as *Annex L*.

Excipients must be pharmacologically inactive and comply with recognized pharmacopeial or food safety & quality standards (e.g., Food Chemical Codex, JECFA). Excipients with known pharmacological effects ("excipients of concern") should be avoided, particularly in products for children. Use of preservatives is not recommended and, if applied, must be scientifically justified. Compatibility studies must confirm that colouring agents, flavourings, coatings, and fillers do not interact with the active ingredient(s) or affect product stability. Use of sugars and other fillers must be evaluated for suitability in sensitive patient groups.

The following documents must be submitted:

1. Specification with pharmacopeial or food standard referenced
2. Certificate of Analysis(s) for all excipients
3. Material Safety Data Sheet (MSDS), if available

2.3. COMPARABILITY BETWEEN INGREDIENTS FROM MULTIPLE SOURCES

The following requirements concern section 2.5 of the IAFPPQ and the supporting documents must be submitted in *Annex R*.

When a manufacturer considers qualifying more than one ingredient supplier, the following approach is recommended:

- At the product development stage, the manufacturer should evaluate different sources of active ingredients and key excipients to establish preliminary compatibility through stress or accelerated studies (typically 8–12 weeks) and to assess equivalency of ingredient sources and formulations in terms of quality and performance. These evaluations should be justified using a risk-based approach considering critical quality attributes and potential variability and the outcomes should guide the selection of suitable sources for scale-up of *preferred formulations*[4] (each formulation with a single declared source of active ingredient) and the design of a source-change comparability protocol.
- At the manufacturing process validation stage, the manufacturer must validate the manufacturing process for the preferred formulation(s) and conduct stability study(ies) for each of the preferred formulations. Given the complexity of multi-micronutrient supplements such as UNIMMAP MMS, which contains 15 vitamins and minerals, it is recommended that process validation focus on a limited number of representative formulations—ideally one or two—to demonstrate process consistency and robustness.
- Post-validation, the manufacturer may introduce new sources of active ingredients or excipients. Such changes will be reviewed by UNICEF and managed in accordance with *WHO Technical Report Series, No. 981, Annex 3: Guidelines on variations to a prequalified product.* At minimum, the manufacturer will need to provide a commitment to place at least one

[4] Preferred formulation means a finished product formula where each of the ingredients come from a dedicated supplier

commercial scale batch with the new formulation on stability study for a minimum of 6 months accelerated conditions and 12 months for long-term at ICH Climatic Zone IVb conditions.

When responding to a UNICEF solicitation, documentation pertaining to the *preferred formulation(s)* must be submitted, along with comparability study report.

For any changes post-LTA, UNICEF must be notified before an ingredient is changed as per Change Management guidance provided in section 4 of this document.

2.4. Intermediates or In-process materials

Intermediate products are partially processed materials that require further manufacturing steps before becoming bulk or finished products, e.g., premixes, bulk coated or uncoated tablets, or any other intermediate form produced either by the finished product manufacturer or a contract manufacturer. The manufacturer must ensure that such intermediates are identified, processed, and controlled in accordance with the principles described in *WHO Technical Report Series No. 986 – Annex 2: Good manufacturing practices for pharmaceutical products: Main principles*.

Intermediates must be clearly labelled with their status (e.g. quarantine, released, rejected) defined and documented throughout the production process. They must be stored under controlled conditions that prevent contamination, cross-contamination, or mix-up. Where applicable, appropriate hold-time stability studies must be undertaken as per *WHO Technical Report Series No. 992 - Annex 4: General Guidance on hold-time studies*. Hold times should not be more than 30 days per processing stage and cumulative hold time should not be more than 90 days, in line with recommendations applied for WHO-Pre Qualification.

The manufacturer(s), including any premix, bulk, or contract manufacturing site(s), should manufacture, identified, processed, packaged, controlled, and handled intermediates as per WHO Good Manufacturing Practices (GMP) and Good Distribution Practices (GDP).

Control must be established to maintain the quality, traceability, and integrity of intermediates throughout processing, storage, transport, and transfer until their conversion into bulk or finished product.

The supplier must ensure that all ingredient and intermediates documentation is obtained from the manufacturer(s) of intermediates and submitted in line with requirements outlined in this document.

3. Finished Product

The following requirements concern section 3 of the IAFPPQ.

When developing a finished product, manufacturers are recommended to refer to the following guidelines:

- *WHO Technical Report Series, 970 – Annex 3: Pharmaceutical development of multisource (generic) finished pharmaceutical products: points to consider*
- *ICH Q8(R2) Pharmaceutical Development*

3.1. MANUFACTURING GMP AND GDP

The following requirements concern section 3.1 of the IAFPPQ.

The finished product must be manufactured and handled as per WHO GMP and GDP guidelines, as detailed in *WHO issued compendia:*

- *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials: volume 1: Good practices and related regulatory guidance, 10th ed*
- *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials: volume 2: Good manufacturing practices and inspection, 10th ed*

General guidance for GMPs and GDPs can be found in the following two guidelines:

- *WHO Technical Report Series, No. 986 - Annex 2: Good manufacturing practices for pharmaceutical products: main principles*
- *WHO Technical Report Series, No. 1025 – Annex 7: Good storage and distribution practices for medical products*

The below mentioned documents must be submitted in *Annex S* of the IAFPPQ.

1. GMP compliance and certification: UNICEF requires that all manufacturing sites involved in the manufacture of the finished product hold a valid drug manufacturing license and be inspected by a Competent Authority. Last GMP audit conducted by SRA, NRA, PIC/S or other competent authorities must be indicated and the cGMP certificate issued by the SRA/NRA must be submitted. The most recent GMP inspection report from the National Regulatory Authority or other agencies listed on the IAFPPQ may be requested, to factor into UNICEF's Reliance Framework for GMP inspections.

2. A summary of ongoing CAPAs: For ongoing CAPAs resulting from non-compliances issued during an inspection by a Competent Authority or procurement agency, a summary of the CAPA with expected completion date must be submitted.

Though not specified in the IAFPPQ, UNICEF may request a copy of the manufacturer's Site Master File (SMF) for review in preparation for conducting a GMP audit. The SMF should follow

- *WHO Technical Report Series, No.961 – Annex 14: Guidelines for drafting a site master file*.

3.2. Finished Product Specification

The following requirements concern sections 3.2 and 3.3 of the IAFPPQ and supporting documents must be submitted in *Annex T* and *U*.

When a monograph for the Product exists, it should comply with all aspects of the current monograph including test methods. For example, Multiple Micronutrient Supplement (MMS) for Pregnant and Breastfeeding women must comply with the *USP monograph Oil- and Water-Soluble Vitamins with Minerals Tablets (latest edition)*; Iron 60 mg tablets must comply with *USP monographs for Ferrous Sulphate Tablets, Ferrous Gluconate Tablets or Ferrous Fumarate Tablets*, or *BP monograph for Ferrous Sulphate* or *Ferrous Gluconate* depending on which chemical form of iron is used.

For guidance on establishing a finished product specification refer to

- *ICH Q(6A) Guideline Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- Manufacturers must maintain a documented risk assessment with appropriate mitigation measures to control impurities and contaminants of concern in ingredients and the finished product, ensuring the product meets its established specifications and acceptance limits.

The following information related to the finished product specifications must be submitted:

1. Copy of the release and shelf-life specifications of the finished product, duly signed by Authorized Personnel (i.e. the person in charge of the quality control or quality assurance department), must be submitted in *Annex T*. Any differences between release and shelf-life tests and acceptance criteria should be justified. Differences for dissolution are not accepted.
2. Analytical method validation report(s), for in-house analytical methods, must be submitted in *Annex T*.
3. Certificate of Analysis (CoA) for the last 3 manufactured batches of the finished product with full qualitative and quantitative analysis of all relevant aspects of the product and in compliance with its marketing authorization and release specifications must be submitted as *Annex U*.

3.3. Manufacturing Process and Process Validation

The following requirements concern section 1.1.4 and 3.4 of the IAFPPQ.

1. Batch formula: The product formulation consisting of complete qualitative and quantitative composition including active ingredient(s) with overage input amounts, and excipients must be submitted in *Annex A*. The quality standard for each ingredient (e.g., BP, USP, in-house) must be indicated and the functionality of each excipient must be explained. The commercial batch size must also be stated.

2. Manufacturing process: A flow diagram and a narrative describing the manufacturing process and manufacturing site, outlining the equipment and detailed processing instructions and controls of critical steps, including tests and acceptance criteria must be submitted in *Annex V*.

3. Process Validation protocol and report: The manufacturer must conduct process validation, including all applicable aspects of validation such as, as per *WHO Technical Report Series, No. 1019 – Annex 3: Good manufacturing practices: guidelines on validation, Appendix 7: Non-sterile process validation and other listed appendices*.

   Process validation must be conducted on at least 2 pilot scale batches (i.e. 1/10th of commercial scale batch size or 100,000 units whichever is larger) and 1 commercial scale batch, with a commitment to repeat process validation study on the next three consecutive commercial scale batches.

   The process validation report must be submitted in *Annex W* and reflect the protocols and procedures followed and include reference to the protocol; reference to the appropriate risk assessment; details of materials, equipment; procedures and test methods; out-of-specification and non-conformance results substantiated with corrective and preventive actions, with appropriate traceability; and a conclusion.

Additional guidance on conducting Process Validation and reporting can be found in:

- *European Medicines Agency (EMA) Guideline on process validation for finished products - information and data to be provided in regulatory submissions*
- *US FDA Guidance for Industry - Process Validation: General Principles and Practices*

3.4. STABILITY

The following requirements concern section 3.6 of the IAFPPQ.

The stability study protocol and consequent report must be submitted in Annex Z and consider the following:

1. Study conditions: Stability studies must be conducted as per *ICH Q1A(R2) Stability testing of new drug substances and drug products,* under ICH Climatic Zone IVb conditions (30°C ± 2°C / 75% ± 5% RH) for each formulation, in final primary packaging. Reduced designs such as bracketing or matrixing may be applied, but the approach must be scientifically justified. Stability studies must be continued for the entire duration of declared shelf-life.

2. Batch selection: The finished product batch used for stability studies should be identical to the commercial batch to be supplied to UNICEF in terms of product formulation, active ingredient sources (i.e., specification and supplier), manufacturing site and packaging format. The supplier must declare ingredient sources used in the Finished Product under stability

studies and commit to conducting stability studies for all intended Active Ingredient sources, additional guidance is provided in section 3.4.1.

3. Number and size of batches: Stability studies should be conducted on at least 2 pilot scale and 1 commercial scale batches, with a commitment to repeat the stability studies on the first 3 commercial scale batches for marketing. Stability study must be conducted for every declared Active Ingredient source.

    a. At least one batch must be commercial scale and the other two may be pilot-scale batches. A pilot-scale batch must simulate full-scale production and be at least 10% of the planned full-scale size or 100,000 units, whichever is larger.).
    b. When possible, finished product batches should be manufactured using at least two different batches of the declared source of Active Ingredients(s).
    c. For actual procurement, preference will be given to products with acceptable real-time stability (ICH Climatic Zone IVb) data from commercial scale batch sizes that cover the assigned shelf-life as specified in UNICEF product specification(s).

4. Attributes tested: The stability testing must cover chemical, physical, microbiological, performance (e.g. dissolution) attributes, including quantification of any added preservative content. Tests should focus on those attributes that are susceptible to change during storage and transport and that can influence the safety, performance and quality of the product.

    For a finished product that is to be reconstituted and/or diluted before use, such as a powder for preparation of an oral suspension or packed in multiple use/dose container-closure system, "in-use" stability data must be submitted to support the recommended in-use storage conditions and duration.

5. Stability report: The stability report must clearly indicate manufacturing details such as the finished product batch formula, active ingredient sources, batch numbers, manufacturing site address, and date of manufacture.

A declaration stating that stability studies have been conducted, or are in progress, with all declared sources of active ingredients must be submitted in *Annex AA*.

Additionally, suppliers should note that:

    a. At least 6 months accelerated stability data and 12 months real time stability (ICH Climatic Zone IVb conditions) data should be submitted at the time of application. Applicants may participate in tenders with less data, with a commitment to continue stability studies and provide routine updates to UNICEF.
    b. Shelf-life extrapolation may be acceptable, and considered for approval by UNICEF, when supported with data and justification in line with *ICH Q1E Evaluation of stability data.*

c. The specifications and test methods used must be described in the stability protocol and report. If the methods are identical to the one described elsewhere in the dossier, a cross-reference will suffice.
d. Stability reports must present numerical values of results for quantitative test parameters. General terms such as, "complies" or "conforms" are not acceptable.

Additional guidance on stability testing protocols can be found in the guidelines below:

- *ICH Q1A – Q1F Stability*
- *WHO Technical Report Series, No. 1010 – Annex 10: Stability testing of active pharmaceutical ingredients and finished pharmaceutical products*
- A useful resource for stability study report template is *UNICEF Stability Study Format Nutritional Supplement*

3.4.1. Stability requirements when changing Ingredient sources

Any post-LTA changes applied to the finished product (as approved by UNICEF) must be handled following:

- *WHO Technical Report Series, No. 981 – Annex 2: WHO guidelines on quality risk management*
- *WHO Technical Report Series, No. 996 – Annex 10: WHO general guidance on variations to multisource pharmaceutical products;* and
- *WHO Technical Report Series, No. 981 – Annex 3: WHO guidelines on variations to a prequalified product.*
- *Section 4 of this document titled Change Management.*

3.4.2. Stability requirements when considering long shipment of intermediates

In case a supplier has a co-manufacturing agreement with another manufacturer/packer, where-in bulk oral dosage forms such as coated tablets are shipped to another site for final packaging, the tablet manufacturer must conduct hold-time stability study when the time for transport, storage and final packaging takes more than 30 days.

Hold-time stability study must simulate transport and storage conditions expected and be undertaken for the estimated duration, considering worst case scenarios. Ideally, the hold-time duration would be less than 3months and no more than 6 months.

The product manufacturer, in this case responsible for final packaging, must test the intermediate bulk product, at receiving, for critical quality and safety parameters as per acceptance criteria set for product release.

For guidance on hold-time stability studies refer to:

- *WHO Technical Report Series, No. 992 – Annex 4: General guidance on hold-time studies.*

3.4.3. Shelf-Life, Transport and Storage

The following requirements concern sections 3.6.3, 3.6.4, 3.6.5 of the IAFPPQ.

1. The finished product's shelf-life must be stated as established based on the complete long-term stability data, conducted at 30°C ±2°C/75% RH ±5% RH (ICH Climatic Zone IVb).
2. Storage conditions, including specific requirements and after-opening instructions must be specified.
3. The product's suitability for use in all relevant ICH Climatic Zones must be indicated.

Transport, transit and storage of products must comply with the following:

- *WHO Technical Report Series, No. 1025 – Annex 7: Good distribution practices for medical products*
- *UNICEF product specifications for product specific requirements*

Additional requirements may be provided in the LTA or PO, such as demonstrated use of data loggers when products are transported or stored under controlled temperature and/or humidity conditions.

3.5. Container-Closure-Systems (or "Packaging")

The following requirements concern section 1.3 of the IAFPPQ.

The container-closure systems include the complete set of packaging components that encloses and protects the dosage form. This includes the primary packaging and/or secondary packaging, where the latter provides additional protection (e.g., light barrier). The container-closure system must be the same as used during the stability study and that will be used for supply to UNICEF, to ensure consistent quality of the product throughout the product's life cycle, including any in-use period.

The packaging material must be suitable for the product, substantiated by a CoA, Certificate of Conformance (CoC), and compliance with recognized pharmacopoeia standards. The submitted documents must contain descriptions and specifications of all packaging components and packaging materials.

At minimum, all products must be packed to:

- Ensure suitability for the intended route of administration
- Include dose measurement/delivery devices where applicable (e.g., droppers for Vitamin D3 drops).
- Provide tamper-evident protection.
- Ensure secondary/tertiary packaging is strong enough to resist crushing and damage during transport and storage.
- Include a Patient Information Leaflet (PIL) or equivalent.

Consideration should also be given to aspects of sustainable procurement, with special emphasis on environmental, social, and economic aspects.

Please refer to the following guidelines when selecting suitable packaging:

- *WHO Technical Report Series No. 902– Annex 9: Guidelines on packaging for pharmaceutical products*
- *EMA Guideline on Plastic Immediate Packaging Materials*
- *USP General Chapter <661.1> Plastic Materials of Construction*
- *USP General Chapter <661.2> Plastic Packaging Systems for Pharmaceutical Use*
- *USP General Chapter <667> Containers—Performance Testing*
- *Ph. Eur. General Chapter 3.2.1. Glass Containers for Pharmaceutical Use*
- *USFDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologies*
- *UNICEF Sustainable procurement procedure*

3.5.1. Primary Packaging

The primary packaging specification must be submitted in *Annex B.*

The primary packaging material used must comply with the following requirements:

1. Materials used in primary packaging must be safe for use with the dosage form.
2. The size of the primary packaging must be proportional to its content.
3. Glass containers must not be more than 250 ml. Glass bottles must be separated by crisscross box dividers or box partitions or be packed individually in cartons.
4. Where applicable appropriate padding should be added to prevent damage to the product during shipment.
5. Container closures should be tamper-evident and have child-resistant closures applied where there is an identified risk to children.
6. Primary packaging must bear appropriate labels, fulfilling minimum labelling requirements as described below in section 3.6 Labelling.

3.5.2. Dose measurement and dose delivery devices

The primary packaging material used for dose measurement and dose delivery devices must comply with the following requirements:

1. Dose measuring devices must be graduated in intervals to allow accurate measurement of all the doses approved for the product.
2. The dosage scales/volumes embossed on dose measurement devices must be in metric units. The use of non-metric units such as “teaspoonfuls” is not acceptable.

3. For oral liquids, compatibility study results confirming suitability of the container-closure product contact materials, including extraction and interaction (migration/sorption) studies, may be requested.
4. For multi-dose containers with delivery devices, suppliers must provide studies demonstrating reproducible dose delivery, along with a description of the container-closure system, materials of construction, and specifications.
5. All delivery devices (e.g., cups, syringes, droppers, applicators) must be securely packed with or affixed to the product to prevent loss, damage, or exposure to unhygienic conditions.

3.5.3. SECONDARY PACKAGING

The secondary packaging specification must be submitted in *Annex C.*

The secondary packaging must be functional, providing additional protection beyond the primary packaging against factors such as moisture, light, oxygen, external contaminants and rough handling during transport and storage. For example, fiber drums or HDPE bottles with an inner LDPE bag, carton outside PVC/Alu blister. The secondary packaging may also be acceptable if they serve as a means to provide a summary of product characteristics/patient information leaflets and/or dosing devices.

The manufacturer must provide information related to the functionality of the secondary packaging in the IAFPPQ as part of the description of package.

For guidance on secondary packaging and labelling, especially for products coming to UNICEF warehouse, refer to:

- UNICEF's *Specifications for packing, packaging and labelling for detailed guidelines on case shipper and pallets*

3.6. LABELLING

The following requirements concern sections 1.7.2 and 1.7.3 of the IAFPPQ.

The product labels must be self-adhesive and preferably made from paper, e.g., pharmaceutical defibred paper (80gsm) that is film coated, and/or UV treated for protection against light and humidity and firmly affixed to be tamper proof and to prevent detachment.

Language:	English and/or French is/are the standard language/s for labels and pack inserts. Additional label languages e.g., Arabic, Portuguese, Russian and Spanish may be requested from time to time. Other local languages specific to the recipient country may be requested with specific tenders and/or PO(s).

Type setting:	Preferably by lithography, in font size 6 point for readability, directly on container/packaging.
Ink and Colour:	The writing on primary and secondary packings must be in indelible ink, preferably in black colour on white background.

A copy of the primary packaging label with artwork and secondary packaging label with artwork must be submitted in *Annex H* and *I*, respectively. For consistency and ease of logistical handling, it is recommended that manufacturers apply the same artwork and minimum labelling requirements, on all primary, secondary and/or tertiary packaging.

The supplier should agree to updating the label, as per UNICEF's and/or importing country's applicable regulatory requirements.

3.6.1. Minimum labelling requirements

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. For suggestions on product specific artwork, containing minimum labelling requirements please refer to UNICEF's product specifications.

At minimum, the product label must include:

1. Name of the product: The name of the product should be written in a clearly visible, bold, large font size. It should identify the dosage form (e.g., tablets, capsules, powder, oral suspension), the WHO recommended name for the product (e.g., INN or INNM) or the pharmacopeial monograph name of the product, and/or the name of the product specified in the UNICEF product specification.
2. List of active ingredient(s): The International Non-proprietary Name (INN) of the active ingredients and strength should be written in a large font size, in bold and must be clearly visible.
    a. If an INN exists for the active ingredient, the English version of the name should be used exactly as published without omissions or abbreviations.
    b. If a Modified INN (INNM) has been published by WHO for the active ingredient(s), it should be used exactly as published without omissions or abbreviations.
    c. If the active ingredient 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 *WHO International Non-proprietary Names Modified*.
    d. If an INN or INNM does not exist, another common name, such as the British Approved Name (BAN) is acceptable.
    e. The amount or percentage of Active Ingredient per dosage unit, unit of volume or unit of weight should be in metric units; next to the name of the active ingredient(s).

3. Names and amounts of excipients: Excipients known to have a recognized action or effect i.e., excipients of concern should be listed (e.g., "contains 10% ethanol", "contains lactose"). The full excipient list must be present in the SmPC and/or PIL.

   For guidance on the list of excipients with known action or effect refer to the European Medicines Agency guideline:

   - *Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use.'*

4. Route of administration: List the route of administration (e.g. oral) and any preparation needed prior to use (e.g. for oral suspensions)
5. Posology and the intended target group(s): Provide the intended dose or serving size and any specific instructions such as "do not chew" or "take after a meal".
6. Pharmacopoeia reference: Pharmacopoeia reference should only be stated where all applicable pharmacopeial ingredient standards and analytical methods were used. It should not be used if in-house standards and methods are used or when more than one pharmacopoeia is referenced.
7. Net quantity per unit pack: Net quality per unit pack should be listed in metric units, must be displayed clearly on each pack level (primary, secondary, tertiary).
8. Storage and handling conditions: The following storage and handling conditions should be listed when applicable.
   a. Recommended temperature (numerical ˚Celsius) during transport and storage.
   b. In-use shelf-life and storage conditions once the product is opened or reconstituted, as applicable.
   c. Statements such as "*Store at room temperature*" or "*This product does not have special storage requirements*" are not acceptable. When required, add statements such as "Do not freeze," "Protect from light," "Store and transport in dry conditions" on primary, secondary and/or tertiary packaging, such that it is clearly legible throughout different stages of the supply chain.

   For more information on the recommended storage statements refer to:

   - *WHO Technical Report Series, No. 1010 - Annex 10: Stability testing of active pharmaceutical ingredients and finished pharmaceutical products*

9. Manufacturing details: The following information regarding the manufacture of the finished product should be included on the product label.
   a. Batch number: The batch number can only consist of up to 10 digits due to limitations in UNICEF's SAP system.
   b. Manufacturing date: The required format is DD/MM/YYYY or DD Month YYYY (where the month is abbreviated or spelled out). The year must be in 4 digits.

c. Expiry date: The required format is DD/MM/YYYY or DD Month YYYY (where the month is abbreviated or spelled out). The year of expiry must be in 4 digits.

d. Name and address of manufacturer and/or marketing authorization holder. For contract manufacture, indicate the name and address of the manufacturer as: manufactured by company X for company Y.

The manufacturing dates, expiry dates and batch numbers should be dynamically printed and consistent in format across primary, secondary/tertiary packaging and SmPC or PIL.

10. GS1 system should be used for barcodes. All information provided in the barcode should be consistent across all packaging levels (i.e., primary, secondary, tertiary).

For guidance and requirements pertaining GS1 labelling and tertiary packaging requirements for supply to UNICEF warehouse, refer to:

- UNICEF's *Updated specifications for packing, packaging and labelling for detailed guidelines on case shipper and pallets*.

Additionally, suppliers should note:

1. The product name should not be misleading with respect to therapeutic effect, composition, or safety of the product. Please refer to the product classification provided in UNICEF product specification.
2. 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.

3.6.2. Patient Information Leaflets and Summary of Product Characteristics

A Patient Information Leaflet (PIL) and/or Summary of Product Characteristics (SmPC) as per WHO standard templates, must be submitted as *Annex J*.

The WHO PQ has standard templates for both detailed and annotated version of information to be included in a PIL and SmPC. These can be found on WHO's website.

At minimum, a PIL must be provided with each product either within the secondary packaging or as part of the label (label booklet or peel-off label) or attached to the top of the primary package. Electronic means of providing information in local languages, such as use of a QR code, is encouraged.

Patient information leaflet (PIL) must include all the necessary information according to the *Directive 2001/83/EC Labelling and package leaflet, articles 54 and 59, WHO PIL template* or other SRA guidance on PIL.

At minimum, the PIL must include:

1. Name of the Medicinal Product – product name, strength, pharmaceutical form.
2. Qualitative and Quantitative Composition – active substances and important excipients.
3. Pharmaceutical Form & Presentation – dosage form, content (weight/volume/units), packaging description.
4. Therapeutic Indications
5. Before You Take This Medicine
   5.1. Contraindications
   5.2. Special warnings and precautions, including hypersensitivity or allergenic reactions
   5.3. Interactions (with food/medicines)
   5.4. Use in special populations (children, elderly, pregnant/lactating, specific conditions)
   5.5. Effects on ability to drive or operate machinery
   5.6. Notable excipients requiring patient awareness
6. Dosage and Method of Administration – dose, route, frequency, duration, instructions for special populations, overdose management.
7. Possible Side Effects – adverse reactions and necessary actions.
8. How to Store the Product – expiry date, storage conditions, special warnings on appearance/handling.
9. Marketing Authorization Holder – name and address.
10. Manufacturer(s)
11. Date of Last Revision

4. Variation Management (or "Change Management")

The LTA holder must notify UNICEF of any changes in the ingredients, manufacturing process, finished product or changes to any other aspects that have been evaluated and approved. Note that a change in manufacturing site will, in addition to change management, also require a new Technical Offer.

Any change(s) must be notified to UNICEF and must be approved by UNICEF in writing, in order to be able to supply the concerned finished product under ongoing or future PO(s).

Post LTA changes are classified into the following three categories, in accordance with *WHO Prequalification Categorization of Variations*:

Major variations: Changes that can have major effects on the overall safety, efficacy and quality of the product. Major variations need to be submitted to UNICEF with all the required documentation prior to implementation.

Minor Variations: Changes that can have minor effects on the overall safety, efficacy and quality of the product. Minor variations need to be submitted to UNICEF with all the required documentation prior to implementation.

Notification: Changes that can have minimal or no adverse effects on the overall safety, efficacy and quality of the product. Notifications are subclassified as annual notification (AN) and Immediate notification (IN).

See references below for guidance on variations and transfer of technology:

- *WHO Technical Report Series, No. 996 – Annex 10: WHO general guidance on variations to multisource pharmaceutical products*
- *WHO Technical Report Series, No. 981 – Annex 3: WHO guidelines on variations to a prequalified product*
- *WHO Technical Report Series, No. 1044 – Annex 4: WHO guidelines on technology transfer in pharmaceutical manufacturing*

The following documents must be submitted as part of the post-LTA change notification covering letter notifying the information and sent via email:

1. A duly filled and signed post-LTA Change Notification Form (Annex II), in searchable PDF formats.
2. A copy of the regulatory approval letter from the local National Regulatory Authority, Regional Regulatory Authority or Competent Authority, if applicable.

ANNEX I: LIST OF MICRONUTRIENT PRODUCTS IN SCOPE

Ascorbic Acid tablets

B complex tablets

Calcium tablets

Ferrous sulphate Oral solution

Folic Acid tablets

Iron and Folic Acid tablets

Iron tablets

Multiple Micronutrient Supplement (MMS) for Pregnant and Breastfeeding Women

Multivitamin oral solution

Multivitamin tablets

Pyridoxine tablets

Thiamine tablets

Vitamin A soft gel capsules

Vitamin D3 drops

Vitamin D3 tablets

ANNEX II: POST LTA CHANGE NOTIFICATION FORM

Post LTA Change Notification form

1. Change overview

1.1. Supplier details

LTA Number	Supplier Name	Supplier Address	Manufacturer Name	Manufacturer Address

1.2. Product details

Product Details	Information to be filled in by the Supplier
UNICEF Material Number	
International Non-proprietary Name including Product strength	
Dosage form	
Shelf life & storage conditions	
Batch size (s)	
Pack type(s) & Pack size(s)	

1.3. Variation type

☐	Notification
☐	Minor LTA change (Minor Variation)
☐	Major LTA change (Major Variation)

1.4. Grouping of Post LTA Changes

☐	Single change
☐	Grouped changes

2. Type of Change and Summary

2.1. Indicate Change name, description, and variation type/number as classified under *WHO TRS 981, Annex 3: Guidelines on Variations to a Prequalified Product*. For example: "Change in batch size of the FPP."

2.2. Provide a summary of the proposed change(s) in the table below. For multiple or grouped variations, the below table must be reproduced for each change.

Current LTA Technical details about the product	Proposed change

2.3. Justification for change(s)

Please provide a technical note justifying the decision to make the proposed change to the product.

2.4. Technical Documentation Supporting Variation

List all technical documents and data supporting the proposed variation, ensuring they address the specific conditions and requirements applicable to the identified variation type.

3. Declaration

I declare that:

I, the undersigned, declare that all the information provided is correct, complete and true to the best of my knowledge.

Name:	
Job Title:	
Signature	
Date:	

Official stamp

ANNEX III: UNICEF'S SUPPLIER QUALIFICATION PROCESS

A simplified process flow diagram below explains UNICEF's Supplier Qualification process for Micronutrient Products.

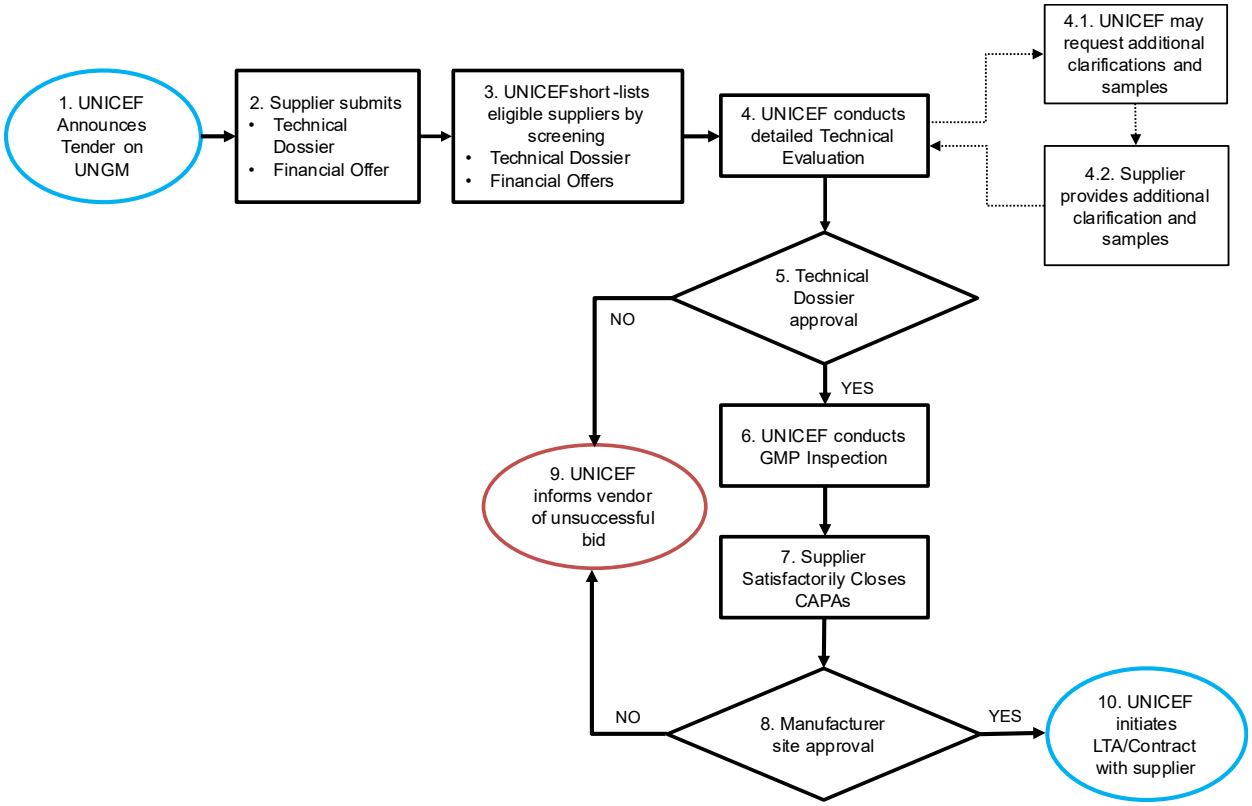

Image 1: UNICEF's Supplier Qualification process for Micronutrient Products.

1. TENDER ANNOUNCEMENT

UNICEF announces tender(s) on the United Nations General Marketplace (UNGM) for all products to be procured. Suppliers must be registered on the UNGM platform and apply to the interested tender via the Procurement Opportunities portal on the UNGM. Refer to *UNICEF Supply | Tender calendars* to stay informed regarding annual tender plans.

2. TENDER SUBMISSION

The tender submission covers two evaluation components: 1) technical dossier, and 2) financial offer.

The supplier must submit completed:

- *Inter-Agency Finished Pharmaceutical Product Questionnaire (IAFPPQ),*
- the *Technical Questionnaire for Pharmaceutical Manufacturers (TQPM)* ,and

- any other com documents listed in the tender.

The filled questionnaires along with supporting documents become the Technical Dossier.

If the supplier is not the manufacturer of the product, they must clearly indicate that in the documents, describe the technical agreements in place with the manufacturer of the product and must ensure that all manufacturing, product and quality related documents are received from the manufacturer. If needed, the supplier must facilitate timely clarifications between UNICEF and the manufacturer.

Technical evaluations will also consider principles of sustainable procurement. Suppliers and manufacturers are expected to integrate sustainable procurement principles across environmental, social, and economic dimensions. This includes completing the relevant sustainability information in the United Nations Global Marketplace (UNGM) and any sustainability-related annexes to UNICEF tender documents, in line with the UNGM Sustainable Procurement Indicators.

Technical evaluation will consider the implementation of ISO 14001 (Environmental Management), with particular attention to waste management, chemical use, and environmental impact. Suppliers without ISO 14001 certification must demonstrate credible progress toward Science Based Targets. In line with waste-reduction objectives, suppliers are encouraged to eliminate non-functional secondary or tertiary packaging without compromising product integrity or essential user information, and to use sustainable packaging that complies with recognized standards, in accordance with UNICEF's Sustainable Procurement Procedure.

Refer to UNICEF Sustainable procurement procedure. *Sustainable procurement procedure | UNICEF Supply Division*

Suppliers must submit their financial offer as part of the tender submission. Financial offers may be considered as part of the screening process.

3. Screening and short-listing of suppliers

Once the tender is closed, suppliers are shortlisted after an initial screening of their Technical Dossier and Financial submission. The screening is intended to evaluate the completeness and adequacy supporting documents provided by the supplier in responses to the questions in the IAFPPQ, TQPM and other tender documents.

4. Finalization of Technical Evaluation

Following shortlisting of successful suppliers, an in-depth technical evaluation of the Technical Dossier is undertaken.

4.1. UNICEF requests additional clarifying information and/or samples

During the in-depth technical review, UNICEF may request the supplier to provide additional clarifying information and/or samples of the product in its final packaging configuration.

4.2. Supplier Provides UNICEF with Requested Clarifying Information and Sample

Suppliers must ensure timely response to clarifications raised by UNICEF and submit supporting documentation, as needed. Product Samples must be labelled as “sample – only for testing” and related shipment documents should indicate “no commercial value”.

Samples must be sent to:

UNICEF Supply Division
Medicine and Nutrition Centre,
Oceanvej 10-12
DK – 2150 Nordhavn, Copenhagen
Denmark

5. Technical Dossier approval

Suppliers whose technical dossiers are found to meet the requirements are advanced to the next stage and contacted to schedule a GMP inspection. If a supplier is unsuccessful, or if the dossier is placed on hold due to incomplete information (e.g., insufficient stability studies), they are informed of the decision and the next steps, as appropriate.

6. UNICEF Conducts a GMP inspection

Following dossier evaluation outcome, UNICEF contacts supplier to schedule a GMP inspection of the manufacturing site(s). GMP inspection scheduling takes into account several factors such as current supplier status with UNICEF and last audit outcomes, PIC/S inspections reports and SRA compliance reports and status.

Supplier(s) must ensure that UNICEF or a designated representative, has access to all manufacturing facilities, including contract sites at reasonable times to perform an inspection. The supplier and/or manufacturer must provide 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 or members of the Inter-Agency partners listed on the IAFPPQ. UNICEF may, upon request, also share the inspection report on a confidential basis with partners listed in the IAFPPQ, as well as The Global Fund and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) inspection authorities. The company will be notified in case such request is received.

The GMP audit is conducted to ensure manufacturers have a robust Quality Management System and to verify compliance with this Technical Requirements document, Good Manufacturing Practices and Good Distribution Practices, as per:

- *WHO Quality assurance of pharmaceuticals: a compendium of guidelines and related materials: volume 1: Good practices and related regulatory guidance*

- *WHO Quality assurance of pharmaceuticals: a compendium of guidelines and related materials: volume 2: Good manufacturing practices and inspection*

UNICEF GMP auditors issue an audit report and any non-conformances observed during the inspection are discussed with the supplier. The supplier must provide a detailed Corrective and Preventive Action (CAPA) plan for all of the discussed non-conformance observations.

7. Supplier CAPA plan closure

The supplier provides UNICEF with regular updates on the CAPA plan implementation. Supplier CAPA plan review continues until all CAPA are successfully closed by the supplier in agreement with UNICEF.

8. Manufacturing site approval

Following satisfactory closure of CAPAs, UNICEF's GMP auditors determine if the manufacturer site is acceptable for the manufacture of the finished product of interest and inform UNICEF's contracting and technical team of the decision.

9. UNICEF informs unsuccessful suppliers

UNICEF contracting team informs unsuccessful suppliers of the tender outcome.

10. LTA/contract establishment

UNICEF contracting team informs successful suppliers of the tender outcome and initiates the process for LTA or contract establishment. All contracts and LTAs follow Common Guidelines for Procurement by organizations in the United Nations, details of which can be found on the United Nations Global Marketplace.

N.B. Exceptional approvals

In exceptional circumstances such as emergencies or market driven limitations, the assessment process and technical requirements described throughout this document may be substituted by a risk-based approach and handled on a case-by-case basis.

In such circumstances, priority is given to suppliers demonstrating regulatory compliance with an SRA/WLA, WHO prequalified or that have been approved by Inter-Agency partners (e.g. MSF, ICRC, WHO).

APPENDIX I: EXAMPLES OF CHANGES AND RELATED MANAGEMENT

Suppliers are responsible for performing a comprehensive, documented risk assessment consistent with WHO and ICH quality risk management and change management principles and guidelines, to determine the potential impact of any proposed change on the safety, quality, and efficacy of a UNICEF approved finished product, prior to seeking UNICEF approval for implementing the change. Suppliers must also ensure that all approved changes are implemented in a controlled and traceable manner. Compliance with these requirements will be verified during UNICEF GMP inspections.

For illustrative purposes, listed below are few examples of how one can apply risk-based change management principles. They examples are not prescriptive and do not represent a defined process or criteria applied in evaluation by UNICEF. Alternative approaches may be acceptable if appropriately justified.

EXAMPLE 1: MANAGING A CHANGE IN PACK SIZE USING A RISK BASED APPROACH

This example illustrates how a reduction in pack size from 100-count to 90-count tablets per bottle can be handled using a risk-based approach. Only the fill count (i.e. the number of tablets in the bottle) is being changed. No other change is being made to the formulation, the primary packaging material, container-closure-system, the desiccant type and amount, the same packaging process and equipment.
This example is described in WHO TRS 981 – Annex 3, 40a.

Conditions to be fulfilled

1. The change is consistent with the posology and treatment duration accepted in the SmPC.
2. Stability data are available for at least three batches of the 100-tablet configurations under long-term and accelerated conditions.
3. Assessment of the existing stability data demonstrates that reducing the fill count from 100 to 90 tablets does not introduce a higher risk of degradation, considering headspace, surface-area-to-volume ratio, and potential exposure to moisture and oxygen.
4. No new or accelerated degradation trend is expected as a result of the reduced fill count.
5. The new pack size is consistent with the approved dosage regimen and duration of use.

Documentation required

1. A completed post LTA Change Notification Form.
2. A written scientific justification that demonstrates the 90-count tablet pack size is comparable to the 100-count tablet pack sizes with respect to stability-relevant parameters, supported by existing stability data and consistent with the approved dosage regimen and duration of use in the SmPC.

3. A summary of existing long-term and accelerated stability data for the 100-count tablet pack size.
4. A commitment letter to initiate stability study with the first commercial batch of 100-count tablet pack size and provide periodic update of stability data till the end of expected shelf life.

EXAMPLE 2: MANAGING A CHANGE IN PACK SIZE USING BRACKETING APPROACH

This example illustrates how a supplier may introduce a new pack size of 100 tablets per bottle using a bracketing approach, where stability data are already available for 60-tablet and 120-tablet bottle configurations. The change may be in fill weight/volume or change in the dimension of primary packaging. The formulation, manufacturing process, primary packaging components (bottle, closure, liner, desiccant type and amount), and finished product specifications remain unchanged.
This change is also described in WHO TRS 981 – Annex 3, 40b2 and 41a.

Note: The use of a bracketing design should only be considered appropriate if it can be demonstrated that the container sizes and/or fills that were selected for bracketing are indeed the two extremes. Bracketing can be applied to studies of the same container closure system where either container size or fill varies while the other remains constant. However, if a bracketing design is considered where both container size and fill vary, it should not be assumed that the largest and smallest containers represent the extremes of all packaging configurations. Care should be taken to select the extremes by comparing the various characteristics of the container-closure-system that may affect product stability. These characteristics include container wall thickness, closure geometry, surface-area-to-volume ratio, headspace to volume ratio, water vapour permeation rate or oxygen permeation rate per dosage unit or unit fill volume, as appropriate.
Refer to ICH Q1D for more details.

Conditions to be fulfilled
In line with ICH Q1D:Bracketing and Matrixing Designs for Stability Testing, the following should be met:

1. Long-term and accelerated stability data are available for at least three batches of the 60-tablet and 120-tablet bottle configurations, in line with stability requirements outlined in section 3.4 of this document
2. The 60-tablet configuration represents the worst case with respect to the headspace per in the container and potential exposure to moisture and oxygen.
3. The 120-tablet configuration represents the worst case with respect to fill mass and tablet-to-tablet interactions.

4. Stability data for the 60-tablet and 120-tablet pack sizes demonstrate comparable degradation trends. Where differences in stability between the extremes are observed, the 100-tablet pack size should be considered no more stable than the least stable extreme, and the assigned shelf life for the 100-tablet pack size must not exceed that of the least stable extreme.
5. The proposed 100-tablet pack size lies between the tested extremes with respect to stability-relevant parameters (e.g. headspace volume, surface-area-to-product volume ratio, moisture and oxygen exposure per unit dose) and does not introduce a new worst-case condition.

Documentation required

1. A completed post-LTA Change Management Form.
2. A written justification describing the bracketing approach and confirming that the 60-tablet and 120-tablet pack sizes represent the quality- and stability-relevant extremes.
3. A summary of existing long-term and accelerated stability data for the 60-tablet and 120-tablet bottle configurations.
4. A risk assessment addressing headspace, moisture and oxygen exposure, surface-area-to-volume ratio and any other stability-relevant packaging parameters. The risk assessment must include a comparative summary of two bracketed size packs and the intermediate pack to which bracketing will be applied.
5. A commitment letter to initiate stability study with the first commercial batch of 100-count tablet pack size and provide periodic update of stability data till the end of expected shelf life.

EXAMPLE 3: INTRODUCING A NEW FUNCTIONALITY IN THE PRIMARY CONTAINER CLOSURE SYSTEM (E.G. CHILD-RESISTANT-CLOSURE)

This example illustrates how a supplier may introduce a new functionality in the primary container–closure system, such as replacing a standard screw cap with a child-resistant closure (CRC). The change to the cap may involve a different mechanical design or locking mechanism (e.g. push-and-turn) affecting the closure components, while the packaging type and material class, bottle and formulation, fill volume, and manufacturing process remain unchanged.
This change is described in WHO TRS 981 – Annex 3, 42a.

Conditions to be fulfilled

1. No change occurs to the primary packaging type or material class.
2. The proposed child-resistant closure demonstrates protective and functional performance that is at least equivalent to the currently approved closure, including

moisture barrier performance, oxygen barrier performance, sealing integrity, and compatibility with the bottle neck finish.

3. The introduction of the CRC does not introduce a new or increased risk to product stability compared with the approved container–closure system.

Documentation required

1. A completed post-LTA Change Notification Form.
2. A documented risk assessment as per addressing functional, mechanical, and barrier-performance risks (e.g. torque range, seal integrity, packaging-line adjustments).
3. Supporting data demonstrating comparability of the proposed CRC to the existing closure, which may include relevant packaging material or performance tests.
4. Detailed information on the proposed CRC, including design and mechanism, materials of construction, specifications and dimensions, and acceptance criteria for torque and sealing force.
5. A stability study summary including results from at least two pilot- or production-scale batches with a minimum of 3 months accelerated and 3 months long-term data; alternatively, where equivalent or superior protective performance is demonstrated, a written justification may be submitted together with a commitment to place the first production-scale batch using the new CRC on long-term stability after implementation.

EXAMPLE 4: CHANGE IN PRIMARY PACKAGING SITE INVOLVING EXPORT OF BULK TABLETS FOR RE-PACKAGING

Description of change

This example illustrates how a supplier may introduce a change in the primary packaging site by transferring coated bulk tablets from a UNICEF-approved manufacturing site to a different facility, potentially in another country or region, for finished product primary packaging operations and labelling (e.g. bottle filling, desiccant insertion, sealing, capping).
This change is described in WHO TRS 981 Annex 3, Change 28b.1.

The coated bulk tablets must be shipped under validated hold-time conditions, stored under controlled conditions at the receiving site, and packaged using the same container–closure system and packaging specifications approved by UNICEF. No changes occur to the batch product formula, manufacturing process, primary packaging materials, packaging type, or finished-product specifications.

Finished-product release testing remains the responsibility of the site authorised in the product dossier as Market Authorization holder.

Conditions to be fulfilled

1. The receiving site for primary packaging has undergone a satisfactory GMP inspection within the last three years by UNICEF, an SRA/NRA, WHO, or another recognised inter-agency partner.
2. The receiving site is appropriately authorised by the relevant NRA to perform primary packaging operations for the pharmaceutical form and product concerned.
3. Transport, storage, and handling of bulk tablets are adequately controlled and supported by validated hold-time data, including appropriate temperature, humidity, and hygienic conditions.
4. Primary packaging operations at the receiving site are demonstrated to be comparable to those of the approved site and do not introduce quality or stability risks.
5. Finished-product release testing is not transferred to the new packaging site unless adequate validated analytical method transfer has been performed and the necessary regulatory approvals are in place.

Documentation required

1. A completed UNICEF post-LTA Change Notification Form.
2. Evidence that the proposed packaging site is appropriately authorised and GMP-compliant, including the current manufacturing authorisation or equivalent NRA-issued document, GMP certificate or statement, and details of the scope and date of the last satisfactory inspection.
3. A signed technical agreement between the sending and receiving sites defining quality assurance, quality control, and finished product release responsibilities.
4. A documented risk assessment addressing the transport of bulk tablets, including transport conditions, container and liner integrity, storage controls at the receiving site, and potential differences in packaging equipment or processes.
5. Information demonstrating comparability of primary packaging operations between the approved and proposed sites, including equipment qualification, key process parameters, and acceptance criteria.
6. A written commitment to placing a production-scale batch packaged at the new site on long-term stability; at the time of UNICEF approval, the finished product should have a minimum of 6 months accelerated and 6 months long-term stability data available.

Note: If the technical agreement between the two sites specifies that the new primary packaging site takes over the responsibility of finished product release testing, then additional conditions must be fulfilled and documentation is required in line with WHO TRS 981 – Annex 3, Change: 29.

EXAMPLE 5: CHANGE IN ACTIVE INGREDIENT SOURCE

This example illustrates how a supplier may introduce a new source (manufacturer or supplier) of an active ingredient in the finished product. The chemical form and the active ingredient specification remain unchanged. No change is made to the finished product formulation, manufacturing process, and finished-product specifications. The change can be to one of more active ingredients.

Conditions to be fulfilled

1. There is no change in the active ingredient specification.
2. The new active ingredient source is shown to be comparable to the current active ingredient source for monograph compliance including identity, strength, purity, and material attributes that may affect finished product quality and stability (e.g. water content, particle size distribution, polymorphic form where relevant, residual solvents, elemental impurities, and relevant impurity profile).
3. A risk assessment supports that the change does not introduce a new or increased risk to the finished product:
    - blend and content uniformity, compressibility/flow, and tablet friability;
    - degradation pathways (especially moisture/oxygen sensitivity);
    - dissolution/disintegration performance.
4. When multiple active ingredient sources are changed concurrently, the supplier may apply with justification, a risk-based testing plan to assess the compatibility of the newly sourced active ingredients for use in the manufacture of the finished product. The testing or evaluation plan may include matrixing if scientifically justified (i.e. stability-critical attributes and quality-critical attributes are not expected to be impacted).
5. The first commercial-scale batch manufactured using the new active ingredient source(s) must be placed on stability to confirm ongoing stability performance under the intended climatic conditions.

Considerations specific to vitamin and mineral finished products

- Minerals: When a mineral active ingredient from a new source complies with the relevant pharmacopeial monograph and the finished-product manufacturer's approved active ingredient specifications, including material attributes that may affect manufacturing and performance (e.g. particle size distribution, hydration state, bulk density, flow properties, polymorphic form where relevant, and elemental impurity profile), the use of more than one supplier may be considered low risk, provided no adverse impact on finished product quality, performance, or stability is observed.

- Pure vitamins: For pure vitamin active ingredients, compliance with the relevant pharmacopeial monograph and the finished product manufacturer's approved active ingredient specifications including material attributes that may affect manufacturing and performance (e.g. particle size distribution, hydration state, bulk density, flow properties,

polymorphic form where relevant, and elemental impurity profile), the use of more than one supplier may be considered low risk, provided no adverse impact on finished product quality, performance, or stability is observed. However, manufacturers should ensure that any differences in the manufacturing process of the pure vitamin active ingredient between suppliers such as route of synthesis does not affect its impurity profile, level of residual solvents, or any stability-critical attributes (e.g. sensitivity to oxidation, light, or moisture) or potential interactions with other ingredients in the formulation.

- Vitamin preparations (e.g. Vitamin A, Vitamin E or other Vitamin preparations): For non-pure active vitamin ingredients supplied as preparations (e.g. beadlets, or coated forms – commonly employed to address solubility and stability limitations), a change in the source of the vitamin preparation is considered higher risk. In these cases, compatibility and comparability studies must be undertaken, for the proposed vitamin preparation to ensure that differences in vitamin preparation composition, manufacturing process, and protective systems (e.g. carriers, coatings, antioxidant systems) do not adversely affect stability-critical attributes and finished product performance characteristics (e.g. dissolution).

Documentation required

1. A completed post-LTA Change Management Form.
2. Current and proposed active ingredient specifications and CoAs.
3. A side-by-side comparison of the manufacturing flowcharts for production of the current and proposed active ingredient, intermediate, or active ingredient starting material (as applicable) at the.
4. A side-by-side comparison of current and proposed active ingredient specifications covering tests for identity and assay; related substances/ impurities; water content/loss on drying (LOD); particle size distribution (PSD); polymorph/crystallinity if relevant; any applicable tests for contamination (e.g. microbiological attributes where applicable; residual solvents; elemental impurities); and any ingredient-specific functional attributes (e.g. coating integrity for beadlets, antioxidant system for vitamin preparations).
5. Process verification evidence demonstrating no adverse impact on product manufacturing and performance (e.g. blend uniformity, in-process controls, tablet hardness/friability, disintegration/dissolution).
6. Stability data to support approval: minimum 3 months accelerated and 6 months long-term, plus a commitment to continue long-term stability to end of shelf life and provide updates as requested.
7. If multiple ingredients are changed concurrently and a matrix approach is proposed for the testing or evaluation plan, submit the scientific justification and stability plan in line with ICH Q1D bracketing and matrixing design principles for stability testing of the finished product.

EXAMPLE 6: CHANGE IN ACTIVE INGREDIENT FORM

This example illustrates how a supplier may change the active ingredient(s) chemical form (e.g. a different salt, ester, complex, or preparation) in a finished product. Such a change can alter the product's quality and performance characteristics and therefore must be managed as a high-risk change. A change in chemical form of the active ingredient is treated as a new product formulation.

Conditions to be fulfilled

1. Scientifically demonstrate equivalence between the current product formulation and the proposed product formulation with the new chemical form of the active ingredient that the change does not affect critical quality attributes, performance (e.g. dissolution or disintegration), or the stability of the finished product.
2. The manufacturing process must be appropriately validated for the formulation containing the new chemical form of the active ingredient.
3. New stability studies must be performed for the formulation containing the new chemical form of the active ingredient(s) form under ICH Climatic Zone IVb storage conditions.

Documentation required

1. A completed post-LTA Change Management Form.
2. The specification, and control strategy for the new chemical form of the active ingredient, including assay expression, impurity limits, and any revised acceptance criteria; and latest CoA.
3. Updated finished product master batch formula and specification, and comparability and performance data demonstrating the impact of the new active ingredient form on product quality, including, as appropriate, dissolution or disintegration, content uniformity, and stability.
4. Process validation documentation (i.e., protocol and report) for the formulation containing the new active ingredient form.
5. Stability data for the new product formulation for at least 6 months accelerated and 12 months long-term (ICH Climatic Zone IVb) as per the stability study requirements specified in section 3.4 must be available at the time of approval.