Quality Manual on Micronutrient Powders

– A Guiding Document –

UNITED NATIONS
INDUSTRIAL DEVELOPMENT ORGANIZATION

HF-TAG Home Fortification Technical Advisory Group

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1. Preamble and Scope of the Document

This Quality Manual on Micronutrient Powders (QMMNP) should give guidance to manufacturers which are interested in the production of Home Fortification Micronutrient Powders (MNPs), as well as to regulators, scientists, and programmers.

Premixes containing micronutrients (vitamins and minerals) have been produced and used for decades for the purpose of industrial food fortification. However, the concept of supplying vitamins and minerals in powder form in single- or multiple-serve sachets to end-consumers for the purpose of mixing into food at home is a relatively new approach, entailing specific requirements for the manufacturers, which are outlined in this QMMNP. The powdered mixture of vitamin and minerals in sachets that are designed for addition to food by end-consumers, i.e. use at the point of use, are hereafter referred to as micronutrient powders (MNP) in this manual.

This QMMNP outlines the requirements for Good Manufacturing Practice in MNP operations, targeting product safety and thus food and consumer safety. This QMMNP should be the basis for the implementation of a reliable Quality Management System (QMS) at the manufacturer.

The entire life-cycle of MNPs shall be covered by the regulations in this QMMNP, from development of the formulation, to the phase of routine operations, until the cessation of the product:

2. About this Document

The requirements outlined in the QMMNP are based on general and specific Good Manufacturing Practice regulations, which are applicable to MNP operations. Nevertheless, the requirements may not be comprehensive under the specific conditions of the individual manufacturer, e.g. local legal or regulatory requirements, or particular requirements such as those for halal or kosher food. It shall be the responsibility of the manufacturer to identify such needs and integrate the respective aspects into the QMS.

The terms used in the QMMNP are based on the definitions in Section 4.
The guidance sections are Sections 5 to 7:

- Section 5
  General Requirements for the Quality Management System for MNP Operations
- Section 6
  MNP Composition and Formulation
- Section 7
  MNP Production (Manufacturing, Quality Control and Storage)

3. Standards and Guidelines

As a general rule, the local legal requirements of the manufacturer's country and the country of distribution are applicable. Furthermore, there are internationally accepted standards and guidelines on which the manufacturer's operations should be based, for example:

- Food safety management systems – Requirements for any organization in the food chain (ISO 22000:2005)
- Home Fortification Technical Advisory Group. Manual on Micronutrient Powder (MNPs) Composition. Geneva: Home Fortification Technical Advisory Group, 2013
- Codex Alimentarius: Hazard Analysis and Critical Control Point System and Guidelines for its application, Annex to CAC/RCP 1-1969 (Rev. 4-2003)
- Codex Alimentarius: Advisory Lists of Nutrient Compounds for Use in Foods for Special Dietary Uses intended for Infants and Young Children, CAC/GL 10-1979, Rev. 2009
- "Food labeling" 5th edition by WHO/FAO 2007

4. Definitions, Abbreviation, Acronyms

Term, Abbreviation, Acronym	Explanation, Definition
Active ingredients	Active ingredients are the raw materials which contain micronutrients (cf. "Micronutrient" and "Raw materials")
ASTM	American Society for Testing Materials
Campaign production	Avoiding frequent changes of product in manufacturing by producing multiple consecutive batches of the same product
CAPA	Corrective and Preventive Actions
Controlled documents	Documents which are issued, distributed, changed and also withdrawn in a controlled manner
CFU	Colony Forming Units (microbial enumeration)
CCP	Critical Control Point
Composition	The composition of an MNP refers to the content of vitamins and minerals (as claimed on the label). There may be different formulations for a given composition; cf. "Formulation"
Cross-contamination	Contamination of one type of product with active ingredients or residuals of another type of product
Critical	Relevant for product safety
Dedicated equipment	Equipment which is exclusively used for the production of one specific type of product. Dedicated equipment is used to avoid the risk of cross-contamination.
EP	European Pharmacopoeia
Excipients	Raw materials contained in products for technological purposes, i.e. carriers and process aids; cf. "Raw materials"
FCC	Food Chemical Codex
Formulation	The formulation of an MNP is the recipe, i.e. it specifies the amount and type of raw materials used for the production of the MNP; cf. "Composition"

Term, Abbreviation, Acronym	Explanation, Definition
GAMP	Good Automated Manufacturing Practice
HACCP	Hazard Analysis and Critical Control Points. HACCP is a system used to identify potential risks for product quality and safety, i.e. food and consumer safety, and to define measures to prevent, eliminate and reduce risks to an acceptable level, and to control risks
Ingredients	Cf. "raw materials"
JECFA	Joint FAO / WHO Expert Committee on Food Additives
Manufacturer	The manufacturer of MNPs, which may be from MNP bulk material to an MNP finished product; cf. Diagram 5
Manufacturing	All processes to obtain the finished product (refer to process-flow in Section 7.2) The structure of the terminology used in this QMMNP is shown in Diagram 1
Material	The term "material" summarizes the starting materials and product
Micronutrients	Vitamins, minerals and trace elements. (Remark: In this document, the entirety of minerals and trace elements is referred to as "minerals")
MNP	Micronutrient Powder MNPs are blends of various nutrients, mainly essential micronutrients such as vitamins and minerals; they are food (supplements) in the sense of Codex Alimentarius. They are intended for addition to food just before consumption. MNPs allow individuals access to fortified foods at the point of use, independent of the availability of/accessibility to industrially produced fortified food. The powders are advantageous for infants and young children, who cannot easily ingest capsules or tablets MNPs are neither therapeutic products nor are they intended to treat or cure diseases, such as severe nutritional anemia. However, they contribute to meeting the micronutrient needs of individuals by improving the nutrient profile of the food. MNPs are not intended to be consumed on their own, but always as fortificants in combination with food. The properties of MNPs should allow mixing with soft, mushy, and semi-solid food. The properties of MNPs should not allow mixing with liquids in order to avoid use for bottle-feeding, which would conflict with the International Code of Marketing of Breast-Milk Substitutes. They shall have high bioavailability, minimal effect on the taste or color of the food to which they are added, and minimal or no interaction with other micronutrients. The UNICEF terminology for MNPs is "Vitamin and Mineral Powders".
MNP Finished Product	MNP sachets in sales units, e.g. cardboard boxes or pouches
MNP Sachets	MNP in individually packaged sachets (single serve or multi-dose)

Term, Abbreviation, Acronym	Explanation, Definition
MNP Bulk	MNP bulk is the term used for the powder mixture of vitamins and minerals in general (in some literature, this is also referred to as "pre-mix-blend"), and in a more specific way for the bulk material, i.e. before dosing into primary packaging material. Refer to structure shown in Diagram 5
NMT	Not more than
NRV	Nutrient Reference Value
Operations	All activities at the manufacturer, comprising quality management, development, sourcing, production, release, transportation, and distribution; as applicable to the steps carried out at the individual manufacturer. Refer to structure shown in Diagram 1
Packaging Material	Packaging material may be differentiated into: • Primary Packaging Material, which has direct contact with the MNP powder and • Secondary Packaging Material, which has no direct contact with the MNP powder
PE	Polyethylene
PET	Polyethyleneterephtalate
Primary Packaging Material	See "Packaging material"
Product	MNP at any stage of manufacturing: MNP bulk material, MNP sachets, MNP finished product Different material codes may be assigned to the different manufacturing stages
Product Safety	All elements related to product quality and consumer safety
Production	All activities required to obtain the finished product: Manufacturing, quality control, release, and storage Refer to structure shown in Diagram 1
QC	Quality Control
QMMNP	Quality Manual Micronutrient Powders; i.e. this document
QMS	Quality Management System
OOS	Out-of-Specification
Raw material	Ingredients of MNPs: active ingredients and excipients Raw materials are chemically and physically specified ingredients, and their individual properties may vary, depending on the manufacturer
RCA	Root Cause Analysis. Method to identify the underlying cause of a non-conformity or deviation
RDA	Recommended Daily Allowance
RH	Relative humidity
Risk	Function of probability of occurrence and severity of a product safety hazard

Term, Abbreviation, Acronym	Explanation, Definition
Risk Assessment	Structured and documented method to identify and evaluate potential risks to product quality and product safety. Ways to eliminate and control the risks should be described
RNI	Recommended Nutrient Intake
Secondary Packaging Material	see "Packaging material"
Shall / should	These signify that compliance with the requirement is expected and mandatory, unless there is a justification that a manufacturer does not have to comply with the requirements. In general, such justification should be based on a risk assessment, and the manufacturer should be able to demonstrate that the requirement can be replaced or fulfilled by an appropriate alternative
Sourcing	"Sourcing" comprises the entirety of activities required to obtain starting material: the selection of suppliers, selection of quality, ordering
SQFI	Safe Quality Food Institute, USA; www.sqfi.com
Starting Material	"Starting material" is everything required for the manufacturing of the product: raw material (ingredients) and packaging material
TE	Tocopherol Equivalent
USP	United States Pharmacopoeia
WFP	World Food Programme

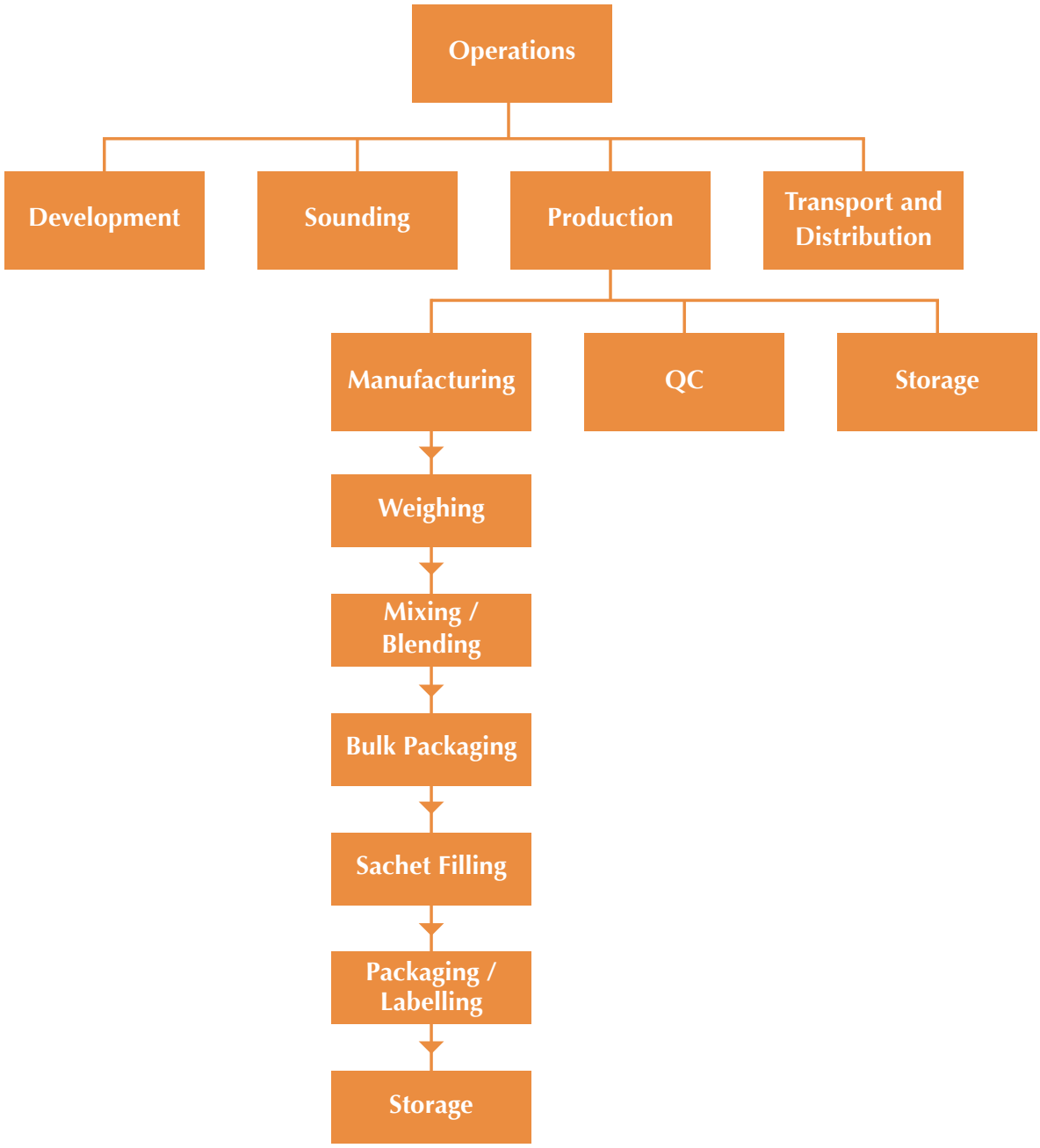


Diagram 1: Terminology Used for MNP Operations in the QMMNP

The diagram outlines the terminology as applied in the QMMNP (e.g. the term "Production" comprises: Manufacturing, QC, Storage). However, the diagram does not reflect an organizational structure or a reporting structure at a manufacturer.

The Quality Management System is an overarching system, which covers all areas of the manufacturer's operations.

5. The Quality Management System

The manufacturer shall establish and maintain a Quality Management System (QMS), which comprises and considers all elements outlined and described in this QMMNP.

The QMS shall be adequate to demonstrate that the manufacturer's operations reliably lead to the product meeting the predetermined quality parameters and, thus, the requirements of product safety.

5.1 The Manufacturer's Quality Manual

The elements of the manufacturer's QMS shall be laid down in a Quality Manual, which is the manufacturer's commitment to product safety.

All operations shall be based on the elements and principles described in the Quality Manual.

The Quality Manual shall include:

the manufacturer's Quality Policy, which shall outline the commitment to product safety, and

details on how the manufacturer establishes and maintains the activities specific to the elements of the QMS. Such details should comprise a description of processes and reference to SOPs, as well as other documents.

The structure of the Quality Manual should follow the structure of the QMMNP.

5.2 Management Responsibility

The management shall be committed to the QMS and there should be documented evidence demonstrating the management's commitment.

It shall be considered part of the management's responsibility to:

- promote awareness for the QMS throughout the organization
- provide adequate resources
- implement structures and functions to enable efficient performance of the QMS
- perform a management review at defined intervals, the minimum being once per annum. The management review shall be based on reports about the performance of the QMS, and shall evaluate such reports with regard to the suitability and effectiveness of the QM, and
- assess opportunities for improvement and the need for changes and support the implementation of such improvement and changes as appropriate.

5.3 Certification of the Quality Management System

Ideally, the MNP manufacturer should be certified to an internationally recognized standard, such as ISO 22000 (HACCP) or an equivalent standard (e.g. SQFI), to ensure compliance with the prospective expectations of international organizations and NGOs, which may be unlikely to purchase MNPs from any suppliers which do not have such certification.

5.4 Resource Management

The manufacturer's operations shall be adequately staffed, which means there should be a sufficient number of personnel with:

- a suitable education
- adequate experience
- technical expertise
- appropriate training, and
- clearly assigned responsibilities, which should be specified in job descriptions (see Section 5.4.2).

Facilities and equipment shall meet the requirements for manufacturing under GMP conditions, as outlined in the QMMNP.

Personal protective equipment shall be provided, and facilities shall be adequately equipped to ensure safe operations and adequate hygienic conditions.

5.4.1 Organization

Organizational diagrams should be in place, and should show details of the current organization.

5.4.2 Responsibilities / Job Descriptions

Job descriptions shall be established for each position or employee. The job descriptions should be available at the personnel department.

The contents shall be, as a minimum:

- the job title (position)
- the objective of the position
- its reporting status (where this position sits within the reporting chain)
- the experience and knowledge required for the position
- tasks
- responsibilities
- competences and permissions
- the reporting line, and
- the date and signature of the employee and the supervisor

5.4.3 Training of Personnel

The knowledge and skills of personnel of all levels shall be commensurate with the requirements of both the tasks and the position, and shall be kept at a state-of-the-art level at all times.

Hence, there shall be a process to:

- implement a general training program, including the frequency of refreshment training (e.g. knowledge about the QMS, general GMP, hygienic behavior)

- identify specific training needs for the individual employee or groups of employees
- define the scope of training
- organize training sessions
- ensure training needs are sufficiently fulfilled and that they document such fulfillment
- adequately check the efficiency of training measures, and
- keep records of the training for each employee and also for temporary personnel and contractors.

Training should and may comprise, as adequate for the individual position:

- regulations related to the QMS
- processes and related SOPs with regard to the manufacturer's operations
- safety regulations
- leadership skills, and
- further training requirements, e.g. language skills, or computer skills.

No employee shall perform tasks in operations without having received training specific to the requirements of the task.

Temporary personnel and contractors should undergo training as required for their specific task.

Training may be performed by internal personnel or by external, qualified trainers.

5.5 Product Safety

5.5.1 General Aspects

Product safety is the essential target of the QMS. The elements to be fulfilled are outlined in this QMMNP.

5.5.2 Quality Risk Management – HACCP Concept

Quality Risk Management is essential to ensure product safety and is a key element in the QMS. Quality Risk Management should be applied throughout the product life-cycle, i.e. from development, through transfer to commercial production and the marketing phase, and should also include product discontinuation.

Risks to product quality and safety shall be assessed by:

1. identifying the risks
2. analyzing the source, and
3. evaluating the risks.

Various tools are available for formal risk assessments. It is recommended that HACCP principles are used and assessed in a systematic and documented way:

- What might go wrong?
- What is the probability that it will go wrong?
- What are the consequences, and how severe are these?

To control risks, adequate measures to avoid or minimize them should be established. If risk assessment leads to the conclusion that an individual risk may be considered to be a residual risk, such risk may be accepted.

Risk assessment tools should be used in particular for qualification, validation, and change control.

Risks should be communicated in the manufacturer's organization to create adequate awareness within those functions involved and concerned.

The Quality Risk Management process should also include the review and potential re-evaluation of previously identified risks and the consideration of new risks.

The manufacturer shall establish a concept by which to identify risks and hazards and control them. This should be done by the implementation of a Hazard Analysis and Critical Control Points (HACCP) system, as adopted by the Codex Alimentarius Commission. A concept of risk assessments, as are, for example, applied for qualification and validation purposes, may be included in the HACCP concept.

Individual and product-specific HACCP programs should be performed as adequate.

Manufacturers should control risks by implementing an HACCP concept. They should:

- **identify** any steps in their operations which are critical to product safety;
- **implement** effective control procedures at such steps;
- **monitor** control procedures to ensure their continuing effectiveness; and
- **review** control procedures periodically, and whenever the operations change (refer to Section 5.8.6).

In general, the seven HACCP principles are:

1. Conduct a hazard analysis
2. Determine the Critical Control Points (CCPs)
3. Establish critical limits and operating ranges
4. Establish a system to monitor control of the CCP
5. Initiate corrective actions when monitoring indicates that a particular CCP is not under control
6. Establish procedures for verification that the HACCP system is working effectively, and
7. Establish documentation concerning all procedures and records appropriate to these principles and their application.

5.5.3 Traceability of Material and Product

Processes and procedures shall be implemented, which make all steps in the manufacturer's operations traceable.

For each batch of starting material, the following information should be available and documented:

- the name and address of the supplier, and (if different from the supplier) the name of the manufacturer of the starting material

- the product name / product code
- the supplier batch number
- the internal batch number
- the date of material intake
- the quantity received vs. the quantity ordered
- the shelf-life (alternatively: Retest-date or "best before"-date), and
- information about the results of quality tests.

The use and consumption of starting material shall be documented in a way that the following information is traceable:

- the product for which the starting material was consumed
    - name
    - code
    - batch
- the product's manufacturing date
- the starting material
    - name
    - code
    - batch
- the quantity of the starting material used.

5.5.4 Foreign Material and Contaminant Control

Foreign material and contaminants are, in general, considered to be a hazard to product safety. Thus, risks of the intrusion of such agents into the product shall be identified and avoided.

Foreign material and contaminants may be brought in via multiple sources. In the production of a good quality product, the utmost effort should be made to avoid such materials, since there are only limited opportunities to remove them.

The table below shows the most common foreign materials and contaminants, their sources, and how to avoid or to remove them, and acknowledges that, in most cases, removal is rarely possible.

Although the supplier of the starting material is responsible for meeting specifications, the manufacturer shall monitor the finished product for foreign material and contaminants.

The manufacturer shall have a specific focus on the risk of microbial contamination; such contamination may be brought in via almost any component or route.

Examples for sources of foreign material and contaminants, and common ways to avoid or remove them, include:

Sources of foreign material or contamination	Contaminants (examples)	Common ways to avoid or to remove foreign material and contaminants (examples)	
		To avoid	To remove
Starting material	- degradation products - metal pieces - plastic material - residuals of packaging material	- sourcing from reliable suppliers (see Section 5.7.3) - clear and comprehensive specifications - incoming material testing - adequate storage	- sieving - metal control with metal detectors and magnets and / or x-ray units
Production aids	- cleaning agents - sanitation agents - disinfecting agents - lubricants	- proper storage (e.g. separation of hazardous material) - adequate use, i.e. use according to supplier's instructions	- cleaning
Equipment	- metal abrasion - gasket material - broken glass - splinters of wood	- adequate equipment (avoiding e.g. glass, wooden material) - maintenance	n/a
Environment	- air-borne particles	- air filtration / clean rooms - closed areas - air-locks	n/a
Environment	- vermin	- pest control - closed areas - air-locks	n/a
Personnel	- skin particles - hair - microbial contamination	- protective clothing - personnel hygiene and hygienic behavior - excluding personnel with skin diseases or contagious diseases from operations	n/a
Product and material mix-up	- wrong labels - wrong product	- clear identification - separated storage - segregated manufacturing areas - clear instructions - closed containers - campaign production	- in a few cases: optical controls, identification and removal of mixed-up material
Cross-contamination	- traces of material from previous batches - traces of starting material from other products	- use of dedicated equipment - cleaning - segregated manufacturing areas - separated storage - closed containers - avoiding dust - campaign production	n/a

Sources of foreign material or contamination	Contaminants (examples)	Common ways to avoid or to remove foreign material and contaminants (examples)	
		To avoid	To remove
Personnel, starting material, etc.	microbial contamination	- hygienic conditions (for more details, see Section 5.8.1) - clothing for personnel - use of clean equipment - limitation of microbial contamination of starting material - low humidity - controlled low temperatures - drying equipment after cleaning - closed containers	- cleaning - disinfection - sterilization

5.6 Documentation

Documentation is the essential way to ensure that the right guidelines, specifications, and instructions are in place, and to provide evidence about the correct execution via the respective records.

Any documents that are part of the QMS should be controlled documents.

The next sections outline the elements of Good Documentation Practice.

5.6.1 Categories of Documents

The term "document" summarizes different categories of document, the most important of which are:

- **SOPs** (standard operation procedures/standard operating procedures) describe general processes and work-flows. SOPs may contain instructions.
- **Specifications** characterize material, equipment, or services.
- **Rationales** provide the background on why things have to be done in a specific way, or why limits are set to a specific level; e.g. risk assessments, HACCP documents.
- **Instructing documents** describe what has to be done, and how. Often, they also contain a rationale on why something has to be done in a certain way, and what has to be recorded; e.g. manufacturing instructions, test instructions, maintenance instructions, qualification plans.
- **Form sheets and protocols** provide room for specific entries. They are, in general, part of an instructing document; e.g. qualification protocol, form sheets for test results.
- **Records** contain results and provide information about what has been done or observed; e.g. manufacturing records, supplier records, analytical results, certificates of analysis, logbooks, temperature records, statistical evaluations.
- **Reports** summarize and evaluate results and data; e.g. qualification reports, development reports.

Documents shall be available for all operations that are critical to product quality.

5.6.2 Control of Documents

To ensure that documents are under control, an instruction shall be in place that describes the handling of documents.

Essential elements of such instruction should be:

- document numbering
- version control
- preparation, review and approval cycles
- date of approval and date for becoming effective, and
- the structure of documents.

Furthermore, document control shall comprise the following aspects:

- an indication should be given about who prepared, reviewed and approved the document
- the title, scope, purpose and area of application shall be clear
- the contents of the documents shall be in clear language; local language is largely preferred
- documents must not be changed without authorization
- responsibility and authority to review and approve documents
- the use of obsolete documents has to be excluded; i.e. obsolete documents have to be withdrawn in an controlled manner
- superseded versions of documents shall be archived to ensure traceability, and
- there should be a regular check of the correctness of the documents, and revision, if necessary.

A list of all current instructions shall be available.

5.6.3 Control of Records

Records shall be available to provide evidence that instructions are followed and operations are under control.

In general, records of quality data shall be checked by a second person to ensure accuracy, completeness, and the plausibility of entries.

An instruction shall be in place, describing the rules of good record-keeping practice. This instruction should outline the following requirements:

- records shall be made concurrent to the performance of the processes
- hand-written entries must be easily legible
- actual observations must be recorded
- pencils must not be used
- entries must be identified with both a date and a signature
- if corrections to entries are required, the original entry must not be made illegible, but shall be crossed out, and the new, corrected entry shall be made

Insofar as electronic records are concerned, e.g. automatic temperature recording, the computer validation requirements shall be adhered to; refer to Section 5.9.

5.6.4 Archiving of Documents

Documents should be archived in access-controlled areas, protected from a negative environmental impact, such as humidity, light, or high temperature. Archiving should allow document retrieval within an adequate period of time. As a general rule, it should be possible to access documentation within 24 hours in cases of emergency, e.g. product recalls.

The archiving time for documentation should be:

- documentation about the development of products: throughout the product life-cycle
- batch-related documents and records: the shelf-life of the product, plus one year
- qualification and maintenance documentation: throughout the life-cycle of the respective equipment
- SOPs, specifications, and instructions shall be archived for a sufficiently long period of time to allow the traceability of the operations, e.g. it should be possible to identify which specification was effective at a certain time reasonably far in the past. As a general rule, 10 years are regarded as sufficient, unless a different period is identified as being adequate or required.

5.7 Product Realization

Product realization comprises all operations throughout the product life-cycle across development, transfer to production, and commercial production, until product retirement.

5.7.1 Customer-Related Processes

In instances where the manufacturer produces for customers, contracts shall be in place. In addition to commercial agreements (e.g. prices, delivery agreements, the handling of proprietary information), contracts should specify all quality relevant subjects, e.g.:

- the specification of the products
- starting material specifications
- processes and operations to be performed with the related instructions
- quality control tests to be carried out
- responsibilities
- handling of changes, and
- communication between the contract partners, e.g. the handling of customer complaints.

5.7.2 Development

The manufacturer should develop products (from MNP bulk formulations to the MNP finished product) in a planned and controlled manner. Documentation shall be kept about all data related and relevant to product development.

The targets of product development should include:

- product safety
- robust processes, reliably leading to product meeting the pre-defined quality criteria, and
- implementation of HACCP principles and concepts.

For details on the development of MNP formulations, refer to Section 6 and, specifically, to Section 6.2.2.

5.7.3 Sourcing

Starting material shall be sourced from known and reliable suppliers. A specific focus shall be laid on key suppliers, i.e. suppliers of critical starting material, such as active ingredient and primary packaging material.

The manufacturer shall have a list of all approved suppliers for all starting materials.

The supplier of starting material is responsible for meeting specifications; however, the manufacturer shall monitor the quality.

5.7.3.1 Supplier Selection, Evaluation and Approval

The following essential criteria should be applied to the selection of suppliers:

- compliance of starting material with specification
- GMP-compliant production
- a low level of risk of product mix-up
- secure supply
- disclosed origin of the starting material
- the availability of process information, as required (e.g. kosher or halal products)

The compliance of the supplier with these criteria should be evaluated on a regular basis. Suppliers fulfilling the criteria can be qualified by the manufacturer as “approved suppliers”.

5.7.3.2 Purchasing

Purchasing shall be done on the basis of approved specifications from approved suppliers.

5.7.3.3 Supplier Certificates

Suppliers should be obliged to provide specific certificates for each batch of starting material supplied.

Such certificates should state all quality critical parameters of the specification, as agreed with the manufacturer.

5.7.3.4 Supplier Auditing

The performance of key suppliers should be audited; a respective procedure shall be in place.

In an audit program, supplier audits should be scheduled on a risk-based approach, and shall include consideration of the past performance of the supplier in meeting quality requirements.

For key suppliers, i.e. suppliers of critical starting material, an interval of one to three years between the audits is, in general, considered to be adequate. Audits should be performed additionally on a non-scheduled basis, in cases where there is specific need.

For less critical starting material, the audit frequency may be lower; an interval of three to five years is acceptable.

During the audits, it shall be checked if the supplier adheres to GMP-standards which are adequate for their production.

5.7.4 Handling of Incoming Material

A procedure for the handling of incoming starting material should be in place.

Incoming material should:

- be registered by means of
  - product name
  - product code
  - internal batch number
  - date of material intake
  - quantity received vs. quantity ordered
  - supplier name, and
  - supplier batch number
- undergo visual inspection to verify the integrity of the material and the correctness of the packaging material
- be checked for availability of a supplier certificate as required, and
- be assigned with a shelf-life.

Starting material should be stored in “quarantine” status before approval by quality control.

If received material is found damaged or cannot be used in production for reasons of quality deficiencies, i.e. non-compliant material, such material should be excluded from use. The material should be returned to the supplier or disposed of adequately (refer to Section 5.10.3).

5.7.5 Manufacturing

For requirements and information with regard to manufacturing procedures, refer to Section 7.2.2.

5.7.6 Qualification and Validation

5.7.6.1 Equipment and Facility Qualification

There should be documented evidence that equipment and facilities perform as they should, which is in general done by qualification.

In order to achieve this, the critical parameters and critical operations of the individual items should be identified. This should be done via a documented risk assessment.

On the basis of the results of this risk assessment, test protocols should be prepared (known as qualification protocols). These qualification protocols shall comprise:

- all parameters and operations evaluated as critical
- a description of how the parameters have to be tested, and
- criteria for the acceptance of these parameters.

The qualification protocols shall be approved and executed after approval. For this, in a field execution step, the described tests shall be carried out and the results shall be documented.

Any deviation from the acceptance criteria shall be documented, evaluated, and remedied accordingly.

If all acceptance criteria are fulfilled, a qualification report shall be issued, which states that the respective instrument or equipment operates according to the requirements.

For more complex systems, qualification may be carried out in different, subsequent steps.

- Design Qualification (DQ) may be the first step, demonstrating that the planned design fulfills the user's requirements. DQ should be performed before purchase of the equipment, to ensure that the purchasing specification complies with the user's requirements. DQ is also, therefore, an important step in terms of economics.
- Installation Qualification (IQ) provides documented evidence about correct installation and the availability of documentation.
- Operational Qualification (OQ) provides documented evidence that the operation is as intended, and the system functions reliably throughout the defined operating ranges.
- Performance Qualification (PQ) provides documented evidence that equipment, facilities and systems, as connected together, can perform effectively and reproducibly, based on the approved specifications.

For existent facilities, a retrospective qualification may be performed, by which the adequacy of equipment and installations for the intended purpose is demonstrated.

5.7.6.2 Process Validation

Manufacturing processes shall be validated to provide documented evidence that the processes, operated within established parameters, can perform effectively and reproducibly, and lead to the product meeting its predetermined specifications and quality attributes.

Quality critical parameters should be identified by means of risk assessments. Based on the quality critical parameters, a process validation protocol shall be prepared for the manufacturing operation. The process validation protocol should contain:

- quality critical parameters
- descriptions of the steps and tests to be performed
- acceptance criteria, and
- samples to be taken.

The quality critical parameters may refer to:

- the quality of the starting material
- process parameters
- quality control points and operations, and
- handling operations.

After approval of the process validation protocol, the protocol shall be executed and the results of the steps and tests shall be documented. Any deviation from the acceptance criteria shall be documented, evaluated, and remedied.

After successful performance of all steps and tests, i.e. when all acceptance criteria are fulfilled, a validation report should be prepared. The validation report should contain a statement that the respective manufacturing processes lead to the product meeting the pre-determined quality parameters, i.e. that the process is validated.

5.7.6.3 Cleaning Validation/Validation of Decontamination Processes

Cleaning processes as described in Section 5.8.1.4 should be validated in a similar manner to the manufacturing processes (refer to Section 5.7.6.3).

In addition to successful cleaning validation, a microbiological monitoring program shall be set up for the entire manufacturing area (refer to Section 5.8.1.5).

5.7.7 Quality Control

A quality control department should be in place at the manufacturer. The quality control department should be responsible for testing starting material and the product, and should perform tests to monitor and control the production environment. In-process controls may be part of the quality control's responsibilities.

In general, Quality Control performs tests on:

- chemical
- physical, and
- microbiological

parameters.

In cases where the manufacturer does not have quality control facilities on site, quality control tasks may be outsourced to third party laboratories. In such instances, contracts shall be in place; refer to Section 5.7.9.

5.7.7.1 Procedures

For the quality control department, documents should be in place for:

- general operations, e.g. the documentation, storage, and handling standards and reference substances, preparation of reagents and standards, cleaning of equipment
- instrument and equipment qualification
- the validation and verification of analytical methods
- analytical procedures
- the handling of OOS-results
- test protocols, and
- specifications.

Key subjects that should be covered in these documents are described in the following sections.

5.7.7.2 Instrument and Equipment Qualification

There should be documented evidence that instruments and equipment perform as they should.

Qualification of analytical instruments and QC equipment should be done in an equivalent fashion to the qualification of production equipment and facility qualification. For more details about qualification, refer to Section 5.7.6.1.

Equipment suppliers may be contracted to support equipment qualification.

5.7.7.3 Validation and Verification of Analytical Methods[1]

The objective of the validation of an analytical method is to demonstrate that the method fits its intended purpose.
For analytical methods, which are published in official sources (e.g. pharmacopoeias), instead of a validation, the shorter process of "verification" can be performed to briefly demonstrate that the application of the method under the given conditions leads to reliable results.
Both the validation and verification of analytical methods shall be carried out with qualified equipment.

Typical validation characteristics which should be considered are listed below:

Specificity
Analytical methods should be specific, i.e. able to unequivocally assess the analyte in the presence of components which may be expected to be present in the sample. Such components are the other ingredients and impurities.

Accuracy (also termed "trueness")
The accuracy of a method shall be determined to obtain information about the "true" value. One way to do this is to apply the analytical procedure to an analyte of a known quantity and determine the recovery, i.e. how much of the known amount can be recovered by the method.

Precision
The precision of a method is validated to determine the degree of scatter between series of measurements obtained under defined conditions, but with defined and known variations; e.g. different days, different analysts.

Detection or Quantitation Limit
When analyzing small quantities of an analyte, e.g. impurities, it may be necessary to determine the lowest amount of the analyte that can be detected (the detection limit), and the lowest amount of the analyte that can be quantified with suitable precision and accuracy (the quantitation limit).

Range and Linearity
Range and linearity should be determined when an analyte has to be quantified in varying concentrations or amounts. The range of an analytical method is the interval between the upper and lower concentrations (amounts) of analyte, for which the analytical method has a suitable level of precision, accuracy, and linearity.

Linearity is given if the readings are directly proportional to the concentration of analyte in the sample.

1. ICH Harmonised Tripartite Guideline
Validation of Analytical Procedures: Text and Methodology Q2(R1), November 2005

For each analytical method, a validation protocol shall be in place, defining the test runs that should be performed to determine the validation characteristics described above, and further conditions, such as:

- equipment (instruments and material)
- chemicals / reagents
- standards, and
- samples.

After successful execution of the validation protocol, i.e. when the analyses have been performed and the results are recorded, the data shall be evaluated and summarized in a validation report, in which the suitability of the method shall be stated.

5.7.7.4 Analytical Procedures

A written procedure should be in place for each analytical method. In general, and as far as applicable, the procedures should, as a minimum, contain information about:

- equipment (instruments and material)
- chemicals and reagents, including information on source, concentration, purity, preparation
- standards or reference substances
- sample preparation
- equipment parameters, and
- the calculation of the results.

There should be an SOP, which describes the preparation of analytical procedures.

5.7.7.5 Test Plans

Approved test plans should be in place for each starting material and product to be tested in QC. In general, such test plans are form sheets, which state:

- the identification of the material (name, material code)
- the characteristics / parameters to analyze
- requirements and tolerances
- an indication as to whether explicit values or only the information “complies” are required, and
- the analytical methods to be applied.

Test protocols shall have sufficient space to document the results.

5.7.7.6 Specifications

Specifications shall be available for each starting material and product. As a minimum, and as far as applicable, they should contain information about:

- the identification of the material (name, material code)
- the source (supplier or in-house production)
- a list of characteristics / parameters, including

- requirements
- tolerances
- the analytical method for determination
- the shelf-life
- storage conditions
- packaging requirements, and
- safety instructions.

Further information may be useful and required, such as unit size, labeling, and transport packaging, as well as information about the risk of undesirable substances (foreign material and contaminants).

An example of a comprehensive specification is shown in Appendix 1.

5.7.7.7 Handling of Out-of-Specification Results

Analytical results indicating that the quality parameters of starting materials or product do not meet the specification are considered to be Out-of-Specification results (OOS-Results). There shall be a procedure describing the handling and investigation of such results, in which the following aspects shall be considered and covered:

Step 1: Investigation of the validity of the analytical result, in order to detect a potential analytical error or sample problem, which would render the OOS-result invalid.

- When an OOS-result is obtained, all material used for the analytical operations shall be kept for further investigation
- A checklist should be available, based on which the laboratory result shall be scrutinized. The check-list should contain questions related to:
  - the use of the right method and material (e.g. instruments, reagents, chemical, glass-ware)
  - adequate training of the technician
  - the correctness of calculations, and
  - any potential abnormalities of the sample.

When the checklist answers indicate that there was an analytical error or sample problem, the OOS-result should be considered invalid and a new analysis should be started.

If there is no indication of an analytical error or sample problem, the next step of the investigation is initiated.

Step 2: Re-analysis of the original sample preparation. (Remark: There are cases in which re-analysis may not be possible or feasible, e.g. a sample preparation may be consumed or aged with regard to the analyte. In such instances, no re-analysis must be performed, but re-testing, Step 3, has to be performed.)

The re-analysis may either confirm the OOS-result or lead to results complying with the specification. In the latter case, an investigation shall be performed to find the reason for the previous OOS-result. Re-analysis results, which are in specification, may not overrule the

previous OOS-result without further investigation. Should it be decided that the previous OOS-result should be disregarded, a rationale should be provided. In any case, an adequate number of re-analysis results should be available; in general, less than six results are not considered adequate.

If the OOS-result is confirmed by re-analysis, the next step of the investigation is initiated.

Step 3: Re-testing of further portions of the sample.

The re-testing may either confirm the OOS-result or lead to results in specification. In the latter case, an investigation shall be performed to find the reason for the previous OOS-result. Re-testing results which are in specification may not overrule previous OOS-results without further investigation. Should it be decided that previous OOS-results should be disregarded, a rationale should be provided. In any case, an adequate number of re-testing results should be available; in general, less than six results are not considered adequate.

If re-testing confirms previous OOS-results, the sample shall be considered out-of-specification and:

- an investigation for the reason shall be initiated in manufacturing, and
- new, additional samples should be analyzed.

Step 4: Analysis of new, additional samples

The analysis of new, additional samples may either confirm previous OOS-results or lead to results in specification. In the latter case, an investigation shall be performed to find the reason for the previous OOS-result. Part of this is the investigation in manufacturing.

Analytical results obtained on new, additional samples, which are in specification, may not overrule previous OOS-results without further investigation and consideration, given that Step 3 confirmed that the initial sample, at least, was OOS. Further investigation is required into the Root Cause of the sample being OOS.

The procedure describing the four steps of investigation should require documentation of each step and the approval of decisions by adequately qualified and authorized personnel. As a general rule, it shall be defined that no OOS-results shall be excluded from the evaluation of starting material or product quality without a rationale or sustainable justification for such exclusion.

The following diagram outlines the work-flow for the investigation of OOS-results:

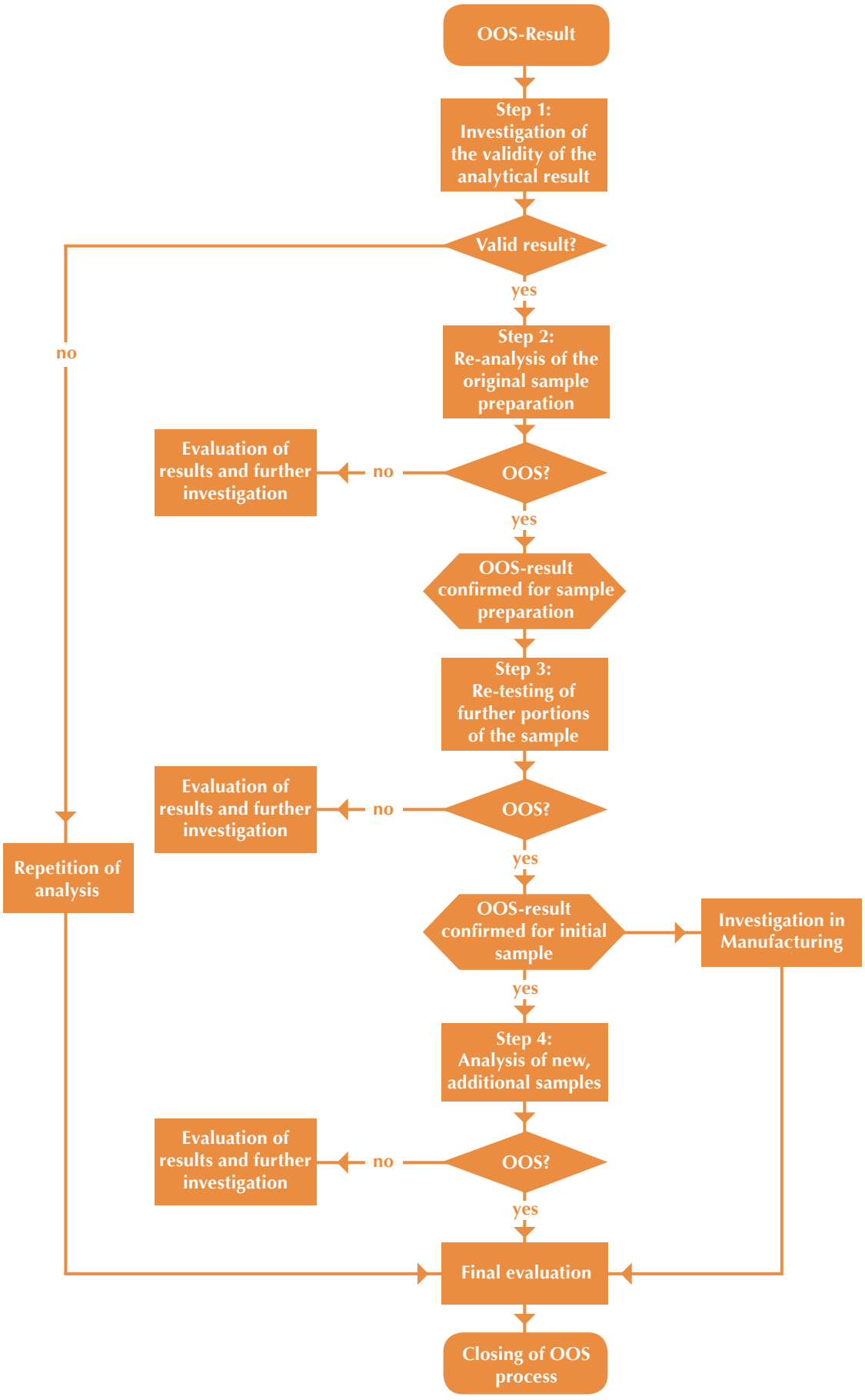


Diagram 2: Work-flow for the Investigation of OOS-Results

5.7.8 Storage

Storage shall be done in a manner that material is protected from any negative impact. The measures to achieve this shall comprise:

- the restriction of access to authorized personnel
- the maintenance of adequate temperature, humidity, and light protection
- the existence of temperature controlled or cold storage areas, as required
- the existence of clean storage facilities
- the unequivocal identification of stored material to avoid mix-up
- only one type of material and batch number being issued per pallet or storage place
- status control, i.e. a distinction between material in status:
    - quarantine
    - released
    - blocked
- the storage of blocked material in separate areas, preferably those which are locked
- the storage of printed packaging material in dedicated locations, ensuring due care to avoid mix-up and to allow reconciliation
- the closure of storage facilities to avoid environmental impact (such as vermin, dust, humidity), and
- the performance of pest control.

If samples of starting material are taken in the storage area, this shall be done under adequate protection, i.e. avoiding contamination of the open containers.

5.7.9 Distribution and Transport

Traceability of the distribution shall be established. Thus, the manufacturer shall keep records of the following information:

- Customer/Receiver
    - name
    - address
- Delivered product
    - type of product
    - batch
    - quantity
- Delivery date
- Information about transport (e.g. transport service provider, route, duration)
- Further information, e.g. commercial information, may be feasible.

Adequate transport vehicles shall be used for distribution. It is assumed that only packaged product will be transported and, therefore, no direct contact with transport vehicles will take place. Nevertheless, transport vehicles should be clean, empty, dry, and odorless.

During transport, the product must be protected from humidity, and unnecessary or long-term exposure to heat should be avoided.

Mix-up with other products shall be avoided.

If third parties operate transport as an outsourced activity, contracts shall be in place (refer to Section 5.7.10).

5.7.10 Outsourced Activities

If services have to be outsourced because they cannot be performed at the manufacturer's site, or if they have to be outsourced to external service providers performing services at the manufacturer's site, written contracts shall be in place for such services. The manufacturer, i.e. the contract-giver, shall be assured that the service provider, i.e. contract-receiver, is capable of performing the outsourced services.

Contracts shall clearly describe the following minimum requirements:

- the services to be provided
- the specifications / instructions to be followed
- ways of documentation and communication
- the responsibilities of the contract-giver and the contract-receiver, and,
- as applicable, the permit for the contract-giver to audit the contract-receiver's facilities.

5.8 Specific GMP-Requirements (Measurement, Analysis, and Improvement)

The following sections give a general indication on operational quality criteria and control thereof. The evaluation of data and results, supported by statistical methods where appropriate, will provide starting points for continuous improvement of the manufacturer's operations.

5.8.1 Production Environment and Hygiene

5.8.1.1 Clean Room Areas

Manufacturing shall take place in areas that provide adequate protection of the product against environmental contamination, and avoid mix-up and cross-contamination.

The areas should be equipped and designed to respect a range of aspects.

- Access shall be via personnel locks and material locks.
- Ventilation should provide adequate temperature and humidity conditions. Temperature should in general not exceed 25 – 30°C and humidity should not be above 60% RH. Other temperature and humidity conditions may be required, due to the specific formulation of the products.
- A contribution to low microbial load may be achieved by air-supply shall with filtered air.
- Walls, ceilings and floors shall have smooth and impervious surfaces, which are easy to clean and allow disinfection. Areas should be free from cracks and open joints, and should not shed particulate matter.

- Rooms shall have adequate lighting. All bulbs and strip lights within product handling areas shall be protected by shatterproof plastic diffusers or sleeve covers or fitted with a fine mesh metal screen.
- Windows shall support adequate lighting of the manufacturing rooms, but it should not be possible to open them. Access should be controlled and restricted to authorized personnel.
- The layout should allow operations to take place in areas connected in a logical order, corresponding to the sequence of the operations, and to the requisite cleanliness levels.
- Floors should have adequate drainage, which should be designed to minimize the risk of contamination.
- Areas should be provided for cleaning utensils.
- Sanitary facilities and refreshment rooms shall be in areas which are separated from manufacturing areas.
- Installations should be easy to clean and arranged so that they do not allow the accumulation of dust, dirt, or other contamination.
- Maintenance workshops should be separated from production areas.
- Separate areas should be provided for tools and parts which are required in manufacturing areas.

5.8.1.2 Staff facilities

Changing rooms of adequate size shall be provided. The changing rooms shall provide sanitary facilities, but should these neither be adjacent to manufacturing rooms nor should direct access be possible from the manufacturing rooms without changing clothing.

Changing rooms should be equipped with:

- lockers for street and production clothing
- cabinets with manufacturing area clothing
- hand-washing, disinfection and drying facilities
- mirrors to check that clothing is correct
- containers for used clothing
- instructions for changing and correct clothing, and
- instructions for hygienic behavior.

There may be office rooms in the manufacturing area.

5.8.1.3 Staff Hygiene

Staff hygiene is mandatory in manufacturing facilities. Personnel should therefore be trained in hygienic behavior, and should follow general standards, which shall be described in instructions:

- no smoking, eating or drinking in manufacturing facilities (drinking water may be provided in designated areas)
- jewelry and wrist-watches must not be worn
- make-up is not allowed in areas where personnel handle open product

- personnel should be adequately equipped to prevent product contamination:
    - garment (coats and trousers or overalls, both preferably without outside pockets)
    - hair-cover/headgear
    - beard-cover as required
    - shoes (or overshoes) specifically designated for the respective area
- in areas where personnel may have contact with the open product, additional protective clothing is required:
    - mouth and nose protection
    - gloves
    - goggles
- material not related to manufacturing shall not be brought into manufacturing areas, and
- personnel with infectious diseases or open lesions on exposed areas of the body must not be engaged in the manufacturing areas.

Adequate clothing and – where required - personal protective equipment shall be provided for all personnel, including visitors.

Washing facilities, in particular hand-washing facilities and disinfectants, shall be provided.

The open product should be avoided as far as possible to avoid potential contact.

The cleaning of garments should be described in procedures or a single-use garment should be utilized.

5.8.1.4 Cleaning and Disinfection

Cleaning and disinfection processes shall be implemented and described in order to achieve a high level of hygiene and product safety.

Potential sources of contamination shall be considered as outlined in Section 5.5.4 “Foreign Material and Contaminant Control” and avoided or removed via adequate processes.

Procedures for cleaning and disinfection (including sanitation and sterilization, as adequate) shall be implemented and should specify, for example:

- the operations to be performed for cleaning and disinfection
- equipment and material to be used for the cleaning or disinfection process
- cleaning, sanitation or disinfecting agents to be applied, including specific instructions for use
- a schedule for the operations
- precise indication which equipment areas have to be treated, and
- any subsequent operations to remove potential residuals.

The cleaning and disinfection agents used shall be Food Industry Use Detergents, approved by the respective agencies. Such agents shall be properly labeled and stored, so that any risk of mix-up with other production material is excluded. Material safety data sheets should be available.

In order to prevent the formation of mold, it is of the utmost importance that equipment is dried after cleaning.

5.8.1.5 Microbiological Environmental and Personnel Monitoring

A microbiological monitoring program shall be established for personnel and the manufacturing area.

For the manufacturing area, the monitoring points shall be determined based on worst-case considerations, i.e. the most critical points shall be selected.

In order to be able to define such points, mapping should be performed, and the locations with the worst results shall be selected as monitoring points.

For personnel working in areas where the open product is handled, the hands and the chest area of the garment shall be monitored.

The following levels are accepted as adequate for areas where the open product is handled:

	Requirement	**Frequency***
Equipment surfaces (after cleaning)	≤50 CFU** / 25 cm^2	quarterly
Floor, walls, ceiling (after cleaning)	≤100 CFU** / 25 cm^2	quarterly
Personnel (in operation)		
Hands	≤50 CFU** / glove (glove print 5 fingers)	quarterly per operator
Clothing: Chest above waist	≤50 CFU** / 25 cm^2	

* Frequency is suggested for routine monitoring. More frequent testing (along with adequate corrective actions) is required if limit values are exceeded.

** No coliform germs must be present.

5.8.1.6 Physical Environmental Monitoring

The temperature and humidity of the production rooms and storage areas should be monitored by recording the conditions; this should be performed on a daily basis at defined critical points.

5.8.1.7 Pest Control

The manufacturer shall take necessary precautions to minimize the risk of pest infestation by preventing access and eliminating potential breeding sites.

In addition to this, a monitoring and control program should be implemented. Monitoring should be performed at defined positions, and the results of the program should be documented.

If fumigation becomes necessary or pesticides must be applied, only approved, food grade agents shall be used, and the activities must not present any risk to product safety. Details about the use of agents and the areas they have been applied to must be recorded.

5.8.2 Maintenance and Calibration

5.8.2.1 Equipment Maintenance

A program of equipment maintenance shall be in place, covering all equipment and installations which are critical to product quality, and instruments controlling or recording quality critical parameters.

Maintenance plans should include:

- equipment identification
- parameters to be checked and maintained
- methods and material to be used
- frequency
- activities to be performed after the maintenance work (e.g. functional checks, cleaning), including acceptance criteria, and
- room for documentation of the results.

If lubricants are used, these shall be approved for use in food-processing equipment.

5.8.2.2 Calibration

A calibration program shall be in place, covering all instruments controlling or recording quality critical parameters. The calibration program may also comprise safety critical instruments.

Calibration plans should include:

- instrument identification
- a definition of reference instruments, including traceability to a national or international standard
- information about the accuracy required
- the calibration interval
- calibration points
- room to document the result of calibration
- instruction related to the flow of information in the event that the adjustment of an instrument became or becomes necessary, and
- instruction on how to indicate the status of the calibration (calibration label).

As calibration provides a retrospective view on the performance of an instrument, the calibration instruction should include the process of “post-calibration”, i.e. calibration of the instruments before they are taken out of operation.

5.8.3 Internal Auditing

A program for internal auditing shall be in place to check the performance of the QMS, and to identify areas for improvement. Such program shall cover

- all operations critical for product quality

and shall provide

- an audit schedule, indicating which area shall be audited at which date.

As a general rule, each area should be audited in a minimum frequency of once per annum. Further audits may be scheduled as appropriate.

Adequately experienced and trained personnel should carry out internal audits. Auditors should be independent of the audited area.

The results of the internal audits should be communicated, and their findings should be reported. As far as findings are concerned, these should be remedied, and the root causes should be identified so that re-occurrence may be excluded in future.

5.8.4 Product Release

The product shall only be released if it meets the pre-defined quality criteria, i.e. the specification.

Adequately qualified personnel shall be authorized to release the product. Product release shall only be done, if

- release testing in quality control confirmed that the product meets the specification. This shall be confirmed by those responsible for quality control

and

- the manufacturing process has been carried out in compliance with manufacturing procedures. This shall be confirmed by the responsible for manufacturing

and

- the quantity of the product awaiting release matches the manufactured quantity.

Should any deviations from the defined procedures have occurred during manufacturing or quality control, these deviations have to be evaluated and actions have to be performed as adequate. Product release may only be carried out if deviations are closed.

5.8.5 Control of Non-Conforming Starting Material or Product

Should there be starting material or product which does not meet the specification, i.e. non-conforming material, it shall be rejected and excluded from use via the following actions:

- identification as being non-conforming
- blocking in the warehouse and separating the product to avoid unintended use
- returning non-conforming starting material to the supplier
- correcting product quality by reworking (refer to Section 5.8.5.1)
- investigating the root cause for the non-conformity in order to exclude future non-conformities of the same origin, and
- if non-conforming product cannot be reworked, rejecting such product, and adequately disposing of it following a defined procedure.

5.8.5.1 Reworking

At any stage of manufacturing, a non-conforming product may be reworked under the following provisions:

- the risks associated with the re-working shall be taken into account when defining the reworking procedure
- the re-working shall follow a defined procedure, which shall be established in a controlled document (re-working protocol) for the individual reworking process
- operations carried out in the course of re-working shall be documented
- the reworked product shall undergo quality control

- if the reworked product meets the specification, it may be released under the conditions outlined in Section 5.8.4.
- should the reworked product not comply with the requirements for product release outlined in Section 5.8.4, it shall be considered to be a non-conforming product and shall be handled according to the process described in Section 5.8.5.

5.8.5.2 Handling of Out-of-Specification Results

Investigation of analytical results which are out-of-specification is an important element under the control of the non-conforming starting material or product. For details concerning OOS-handling, refer to Section 5.7.7.7.

5.8.5.3 Complaint Handling

All complaints received by the manufacturer shall be handled according to a defined procedure. This procedure should contain the following elements of complaint handling:

- documentation of
  - the name and address of the complainant
  - the product
  - the batch number
  - the date when the complaint was received
  - the cause of complaint
  - further information as available and relevant (e.g. the means of distribution, specific information given by the complainant).
- Complaints shall be handled as deviations (refer to Section 5.8.7).
- Reference to retention samples should be made as appropriate, in order to compare the quality of the product which is being complained about with the quality of the product which is being retained (refer to Section 7.3.7).
- A reply shall be given to the customer within a reasonable time frame.
- Overall documentation and the evaluation of complaints in order to enable the identification of repeated complaints about the same product or for the same reason.

5.8.5.4 Product Recall

Should a product be on the market which is found to be non-compliant, a recall may be required. A recall procedure shall therefore be in place.

The procedure should contain the following instructions and regulations:

- the function and name of the person responsible for the recall process. Suitable deputies should be named
- the decision-making criteria for the initiation of a product recall
- the way to identify the non-conforming product and batch, including the evaluation of consequences to other products or other batches of the same product
- traceability of the means of distribution shall enable the manufacturer to identify the destination, i.e. the first external customer of the product or products to be recalled

- description of the way in which the recalled product should be received, stored (separated from other products) and disposed of
- the flow of information to authorities and public which may be required, based on the severity of the recall, and
- any local regulatory requirements relating to product recall procedures must be met, and shall override internal procedures when necessary.

The manufacturer shall have a list of personnel who can handle a recall situation at any time. This list shall include names and functions, as well as emergency telephone numbers; at least two of the nominated persons shall be accessible continuously (24 hours a day/seven days a week.)

To ensure that the recall process runs smoothly when required, the procedure shall be tested in mock runs. The annual performance of mock-runs is recommended. The results shall be documented and reviewed for their improvement potential.

5.8.6 Change Control

The Change Control system shall ensure that any intended changes are requested in writing, and are assessed for their potential impact on product quality and product safety. The assessment should be performed by an interdisciplinary team, which has the necessary competence to evaluate the potential impact of a change in a broad perspective. The evaluation should be followed by the definition of appropriate measures and actions to avoid or minimize potential impacts.

Changes which have a potential impact on quality include, but are not limited to:

- equipment and facilities
- processes and methods in the manufacturer's operations
- starting material, including manufacturers or suppliers thereof
- outsourced activities
- legislation and guidelines.

The consequences and effectiveness of changes with a major impact should be monitored after implementation, in order to allow the identification of unintended impacts.

5.8.7 Incident and Deviation Management

In the manufacturer's operations, incidents may occur and a procedure should be in place to handle incidents.

It is the nature of incidents that they are unplanned and unpredicted. Incidents may be of different natures and may

- not present a violation of existing procedures or limit values. If so, they should be recorded as remarks in quality related documents and should be considered when performing quality evaluations.
- present a violation of existing procedures or limit values. If so, they shall be handled as deviations. (Examples include deviation from defined room temperature, deviation from microbiological limits, or deviation from processing parameters.)

Deviations shall be recorded in precise wording by the department where the deviation has happened or has been observed. The subsequent evaluation of the impact on product quality should be carried out under the involvement of QA representatives.

As a general rule, there is a reason behind every deviation. This reason, or underlying cause, is called the “Root Cause”. A crucial part of deviation management is the Root Cause Analysis (RCA) (refer to Section 5.8.8).

If a deviation occurs, it is in general followed by:

- immediate actions which remedy the immediate impact. Such immediate actions could be, for example:
    - interruption of the operation
    - separation of the affected product
    - the removal of spilled material.
- RCA (refer to Section 5.8.8)
- Corrective actions (refer to Section 5.8.9)
- Preventive actions (refer to Section 5.8.9)

Deviations linked to specific batches should be closed before such batches are released (refer to Section 5.8.4).

5.8.8 Root Cause Analysis

The manufacturer should have a procedure to perform an RCA. This may be carried out in different ways. It should include the following elements and considerations:

- the process and results should be documented
- signature by the participants
- the adoption of a broad perspective by means of considering the entirety of potential impact factors, such as:
    - material
    - equipment
    - operational processes
    - personnel
    - organization, or
    - environment.

There may be cases where the root cause cannot be identified unequivocally. In these instances, the most probable cause or causes shall be assumed when defining subsequent actions.

5.8.9 Corrective Actions and Preventive Actions (CAPA)

The management of corrective actions and preventive actions (CAPAs) should be defined in a procedure. CAPAs should be based on the result of the RCA (refer to Section 5.8.8).

Corrective actions are taken to eliminate the cause of a deviation and thus to prevent re-occurrence.

Preventive actions are taken as a measure to prevent the occurrence of a risk or a specific deviation.

A system should be in place to follow up on the effectiveness of the corrective and preventive actions.

5.9 Computerized Systems

If the manufacturer's operations or parts of the operations are controlled or supported by computerized systems, and these perform or document critical parts of the operations, the computerized systems require validation. Examples of computerized systems which are involved in critical operations include:

- Manufacturing Execution Systems (MES)
- System Control and Data Acquisition Systems (SCADA)
- Enterprise Resource Planning Systems (ERP-Systems)
- Laboratory Information and Management Systems (LIMS)
- Building Management Systems (BMS)

If and to what extent systems such as the systems above perform critical operations should be identified by the manufacturer.

Based on this criticality evaluation, the systems require computer validation. Computer validation should be performed on the generally accepted standard of Good Automated Manufacturing Practice (GAMP).[2]

5.10 Environmental Management

The manufacturer's organization shall act responsibly, and make every reasonable effort to protect the environment.

5.10.1 Resource Management

The manufacturer shall encourage the organization to use resources prudently, avoiding the waste of personnel resources, energy, starting material, and other consumables.

Awareness of the value of any kind of resources should be created.

5.10.2 Energy Management

An overview of energy requirements and consumption should be available. This should provide the knowledge basis for continuous improvement and energy saving.

5.10.3 Waste Management

Adequate systems shall be in place for the collection and appropriate disposal of waste. The disposal of waste shall be in compliance with local regulations, and shall respect the requirements for environmental safety.

Waste containers shall be properly identified, and no waste shall be accumulated in production areas.

2. GAMP 5: A Risk-Based Approach to Compliant GxP Computerized Systems

6. MNP Composition and Formulation

This section outlines the specific requirements with regard to the composition and formulation of MNPs. It covers the scope of development, manufacture, and quality control.

Information about the recommended composition of MNPs (e.g. the vitamin and mineral content requirements), target groups, and programmatic experiences may be found in current HF-TAG resources:

1) Manual on Micronutrient Powder (MNPs) Composition. Geneva: Home Fortification Technical Advisory Group, 2013.

2) HF-TAG MNP Programmatic Guidance Brief: Programmatic Guidance Brief on the Use of Micronutrient Powders for Home Fortification. Home Fortification-Technical Advisory Group (HFTAG); 2011.

3) Home Fortification with Micronutrient Powders (MNP). Sight and Life on behalf of Home Fortification-Technical Advisory Group (HFTAG); 2013.

However, in order to provide more explicit guidance for manufacturers, one standard MNP formulation for infants and young children aged from six to 23 months, which is also suitable for 24 to 59-month-old children, is given as an example in the sections below. The composition is based on the composition outlined in document (1) above.

6.1 Composition

MNP compositions have been used with up to 16 micronutrients.

The commonly used reference for the content in an MNP sachet is the joint statement by WHO/UNICEF/WFP, published in 2007, which proposes daily supplementation as detailed in the table below, in which some recently made adaptations have also been considered.

Micronutrients		**Amount in MNP for Children**[1]
Name	**Unit**	6 – 23 months (24 - 59 months)
Vitamin A (RE)	µg	400
Vitamin D3	µg	5.0
Vitamin E (TE)	mg	5.0
Vitamin C	mg	30
Thiamine (Vitamin B1)	mg	0.5
Riboflavin (Vitamin B2)	mg	0.5
Niacin	mg	6.0
Vitamin B6	mg	0.5
Vitamin B12	µg	0.9
Folic Acid [2]	µg	90
Iron	mg	10
Zinc	mg	4.1
Copper	mg	0.56
Selenium	µg	17
Iodine	µg	90

[1)] Manual on Micronutrient Powder (MNPs) Composition. Geneva: Home Fortification Technical Advisory Group, 2013

[2)] Equivalent to 150 µg Folate

Modifications in composition (e.g. MNPs which do not contain all of the above mentioned micronutrients or further micronutrients, e.g. Vitamin K) may be required to follow new scientific evidence.

Manufacturers should select compositions which are recommended by internationally acknowledged guidelines.

6.2 Formulation

6.2.1 Example Formulation

The following table contains a possible formulation for the composition outlined in Section 6.1. The formulation meets the requirements of the UNICEF procurement specification for an MNP with a shelf-life of 24 months at a storage temperature of a maximum of 30°C.

MNP 1 g sachet, Target group: Children 6 – 23 months (24 – 59 months)
UNICEF procurement specification; product shelf-life 24 months; storage temperature 30°C

	Unit	Label declaration per sachet (1 g)	Overage in % of label declaration	Quantity in formulation per g	MNP Bulk		MNP Sachet		**Raw Material**	
					Min limit per g	Max limit per g	Min limit per g	Max limit per g	Quantity g / kg	Ingredient
Micronutrients									**Active Ingredient**[1)]	
Vitamin A	µg RE	400	45 %	580	522	667	360	667	5.949	Dry Vit. A acetate , water-dispersible beadlet
Vitamin D3	µg	5.0	50 %	7,5	6.75	8,625	4.5	8.625	3.000	Dry Vit. D3, water-dispersible beadlet
Vitamin E	mg TE	5.0	12 %	5.6	5.04	6.16	4.5	6.16	16.688	Dry DL-alpha-Tocopheryl-Acetate 50%
Vitamin B1	mg	0.5	40 %	0.7	0.63	0.77	0.45	0.77	0.864	Thiamin mononitrate
Vitamin B2	mg	0.5	45 %	0.725	0.653	0.834	0.45	0.834	1.036	Riboflavin 5'-phosphate-Sodium[2)]
Vitamin B6	mg	0.5	30 %	0.65	0.585	0.715	0.45	0.715	0.790	Pyridoxine hydrochloride
Folic Acid	µg	90	35 %	122	109	140	81	140	1.215	Folic acid 10% dilution
Vitamin B12	µg	0.9	35 %	1.215	1.094	1.397	0.81	1.397	1.215	Vitamin B12 0.1% spray-dried
Vitamin C	mg	30	15 %	34.5	31.05	37.95	27	37.95	34.500	Ascorbic acid fine powder
Niacin	mg	6.0	30 %	7.8	7.02	8.58	5.4	8.58	7.800	Niacinamide
Iron	mg	10	10 %	11	9.9	12.1	9	12.1	58.164	Ferrous Fumarate, 60% coated
Zinc	mg	4.1	10 %	4.51	4.059	4.961	3.69	4.961	36.196	Zinc Gluconate
Copper	mg	0.56	20 %	0.672	0.605	0.739	0.504	0.739	4.803	Copper Gluconate
Selenium	µg	17	50 %	25.5	20.4	30.6	15.3	30.6	5.843	Sodium Selenite 1% on $CaCO_3$
Iodine	µg	90	30 %	117	93.6	140.4	72	140.4	1.575	Potassium Iodide
Excipients									**Excipients**	
Maltodextrin	not applicable								805.362	Corn Maltodextrin DE 11 - 14
Tri-Ca-Phosphate									10.000	Tri-Calcium Phosphate, FCC
SiO2									5.000	Silicon Dioxide
Sachet weight: 1.0 g; limits 0.9 - 1.1 g										

[1)] Weights refer to the active ingredient and not to the micronutrient. For conversion factors, refer to Sections 6.3.1 and 6.3.22) Limits expressed as Riboflavin

6.2.2 Formulation Development

The formulation of MNPs is influenced by multiple factors. The following sections list and explain the most important criteria to be considered.

6.2.2.1 Flow Characteristics

The flow characteristics of starting materials and thus the resulting MNP powder are important factors for the homogeneity of the product.

Good flow ability is needed for proper mixing and, especially, filling into the final packaging (sachets); however, it has to be kept in mind that excessive flow ability might lead to de-mixing of the MNP powder, potentially resulting in a non-homogenous formulation.

As a general recommendation, starting material with low hygroscopic properties should be used. Processing aids may be added to decrease the stickiness and adhesion of the MNPs.

For example, Tri-Ca-Phosphate and Silicone Dioxide are employed to improve flow characteristics. Nevertheless, there are interdependencies between the carrier (e.g. Maltodextrin) and the ingredients being used to improve flow properties. Furthermore, adequate flow characteristics also depend on the specifics of the processing equipment. The excipients mentioned here are not expected to impact on MNP taste.

6.2.2.2 Bioavailability

Bioavailability, especially the bioavailability of minerals, may vary depending on the chemical form, particle size, and surface. However, in the food to which the MNPs are added, additional factors, such as absorption inhibitors or enhancers, may influence the bioavailability substantially. Mineral salts, which have high bioavailability in the absence of inhibitors, may become less bioavailable in the presence of an inhibitor, while others are not affected by an inhibitor.

This is the case, for example, for water-soluble iron forms versus chelated iron forms. The optimal choice of minerals are those that are easily absorbed and do not change the taste or color of the food to which they are added. Various forms, including microencapsulated forms of minerals, have been successfully used in MNPs. Chelated forms of minerals, such as NaFeEDTA, are particularly suitable when added to high fiber, phytate or tannin containing foods.

Mineral salts which are not soluble either in water or mineral acids, should not be used for MNPs. For acid soluble iron salts, small particle sizes (very fine milling, particle size ~3µm) substantially increase the bioavailability, due to improved solubility in the gastric juice.

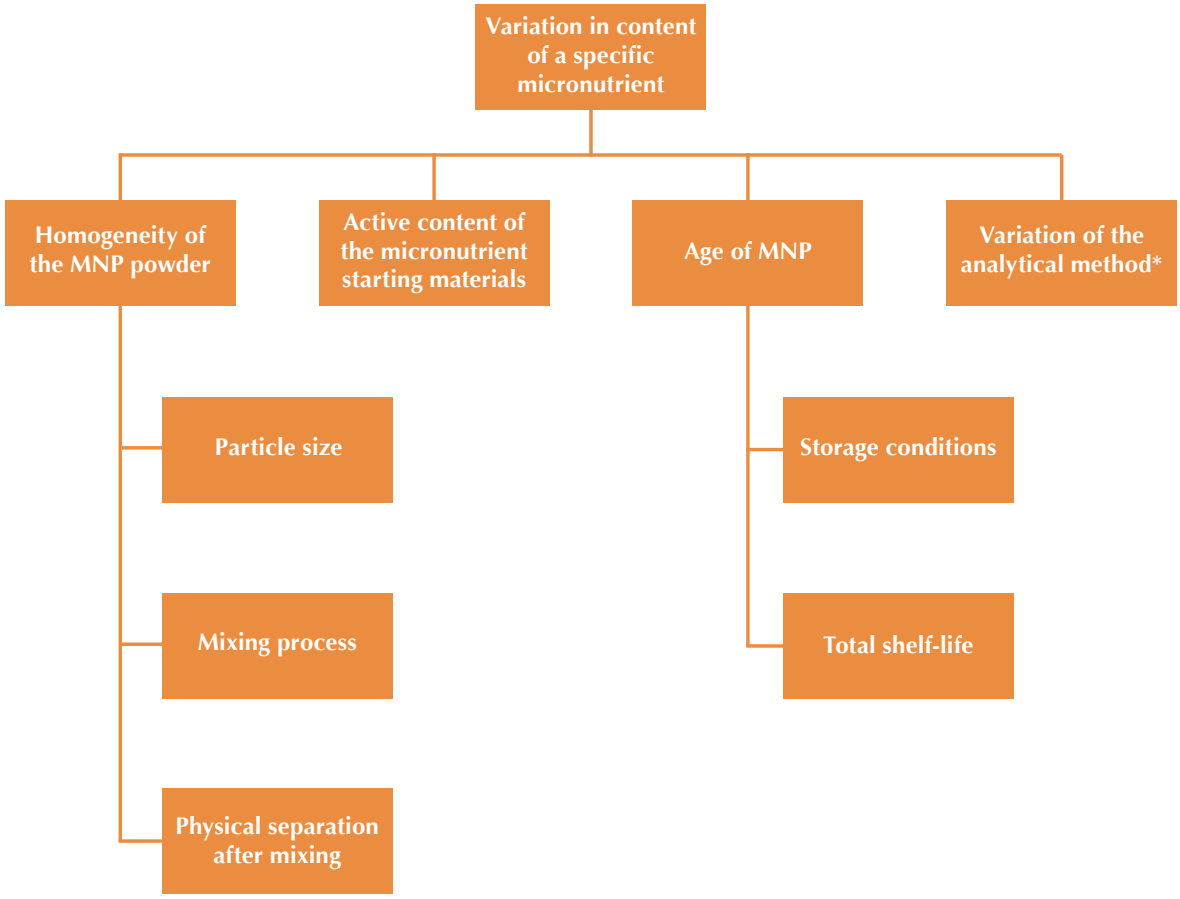
The coating of micronutrients may have a positive impact on taste, but may have a negative impact on bioavailability, which should be considered when selecting the coating material.

6.2.2.3 Variation in Content – Content Uniformity

The content of micronutrients per MNP-sachet may vary for different reasons:

- the homogeneity of the MNP powder, which may vary for different causes
- the active content of the micronutrient starting material, and
- the analytical variation of validated methods (i.e. specific and adequately sensitive).

The diagram indicates the reasons for variation in an overview. Further details are given in the text below. In conclusion to these considerations, the best-case total variability for freshly produced MNP powder may be assumed as ±10%.



* Analytical method should be specific and sufficiently sensitive, which should be demonstrated by validation

Diagram 3: Causes of Variation in Micronutrient Content in MNP Sachets

Particle Size and Resulting Content Uniformity:

The particle size of the active ingredient is of principal importance, although there is no general rule for the optimal particle size of the active substances for MNP powder formulations.

An advantage of a high number of particles, corresponding to a small size of particle, is that it may improve bioavailability.

Another advantage of small particles is improved homogeneity, which can be achieved due to the higher number of particles. This is of specific importance for products with a low concentration of micronutrients, or when the individual micronutrients in an MNP power differ considerably in their quantity.

The more particles, the lower the variation coefficient of the specific micronutrient, which can be explained for distribution reasons:

$$CV\% = \frac{100}{\sqrt{N}}$$

N = number of particles of an individual micronutrient per serving.

CV% = Variation Coefficient of content uniformity

As a general rule, the importance of the small particle size is low when the quantity of a micronutrient is high in the MNP; this is high when the quantity of a micronutrient is low in the MNP.

The variation coefficient for the content uniformity should be below 1%; thus, 10,000 particles of each micronutrient should be contained per serving, assuming a serving size of 1g.

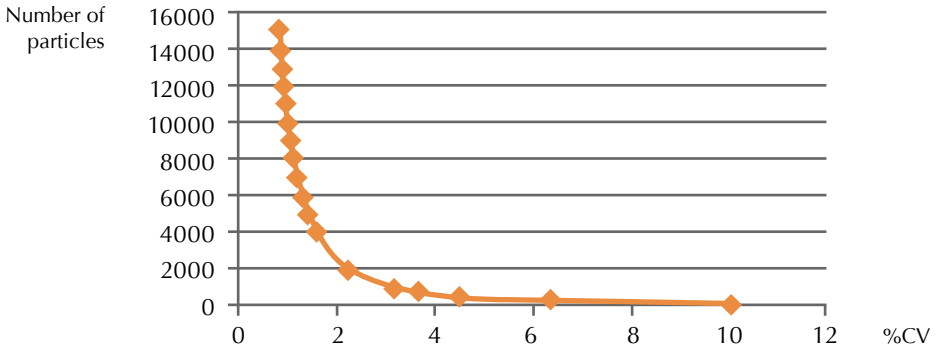


Diagram 4: Dependency of Variation Coefficient of Content Uniformity on Number of Particles

The content uniformity issue is of especial importance for the selection of the right vitamin A, D, B12, and selenium form.

For improved content uniformity, either beadlets or spray dried product may be used:

- Beadlets: » 50,000 particles / g, with a diameter of 200 – 300 µm
- Spray-dried product: > 1,000,000 particles / g

In some cases, quantities are very low (B12/Se), as such. In these cases, pre-fabricated dilutions (triturations) may be used.

Alternatively, more stable active ingredients with larger particles (e.g. Vitamin A or Vitamin D beadlets) may be employed. Another option to improve content uniformity is the use of spray-dried formulations (e.g. Vitamin A or Vitamin D).

For low dosed active ingredients (e.g. 100 µg Vitamin A), only spray-dried product forms should be used; for higher dosed active ingredients (e.g. 400 µg), beadlets may be chosen.

Mixing Process

The process of mixing the ingredients has an impact on the homogeneity of the MNP powder. Homogeneity may be influenced by:

- mixing intensity
- mixing time
- the geometry of the blender
- the material of the blender, and
- the physical properties of the starting materials.

Thus, the parameters which lead to optimum homogeneity have to be determined for the individual conditions. It should be taken into account that inadequate mixing parameters, e.g. excessive intensity or duration, may lead to de-mixing.

Physical Separation after Mixing

Various parameters may lead to physical separation of the MNP powder, i.e. components, which were homogeneously distributed, may separate again. Among these parameters are:

- transportation / physical stress, and
- the physical properties of the ingredients (e.g. electrostatic loads or particle size).

Thus, not only the physical properties of the starting materials, but also the aspects of proper handling after the mixing process, should be taken into account at the manufacturer's operations.

Content of Active Ingredient in Micronutrient Starting Material

The content of active ingredient in the individual starting materials may vary due to different manufacturing conditions of the starting material, e.g. its water content or the content of active ingredient in pre-fabricated dilutions. The contribution of variations in potency range should be low; thus, for each batch of starting material used for MNP manufacturing, the content of active ingredient should be known, and only batches that comply with the starting material specification shall be used.

Analytical Variation

Another factor contributing to the total variation is the analytical variation. Each analytical method has a specific precision, which shall be determined during the validation of the analytical method (refer to Section 5.7.7.3)

6.2.2.4 Taste

Due to the given characteristics of the individual micronutrients, it is not possible to create a totally tasteless product. However, it is possible to minimize a negative taste impact in such a way that the MNP is well accepted.

The taste impact may be caused by:

Vitamin B1	A slightly "soupy" or "yeasty" taste
Vitamin B2	This is slightly bitter for bitter-sensitive persons
Ascorbic acid	Slightly acid
Iron, Zinc and Copper salts	Metallic; the level of perception of this depends on its solubility in fortified food. E.g. Fe-Pyro-phosphate has a better taste than Fe-Fumarate or NaFeEDTA. The taste of ZnO is better than the taste of Zn-Gluconate or Zn Sulfate. Coated mineral salts may be used to contribute to a bland taste.

The use of coated active ingredient forms will mask the unpleasant taste of some minerals and vitamins. Coated Fe-Fumarate, for example, has been used successfully and extensively in MNPs.

However, taste masking is only of value when the MNP is added to foods that are at or near to room temperature. When the MNP is added to hot products (temperatures >60°C), the coating will melt and thus lose its effect.

If coated active ingredients are used in the formulation, it should be clearly noted on the instructions for use that the MNP should only be added to food that has been cooled after cooking (to < 60°C).

6.2.2.5 Color

Vitamins and minerals give MNPs a white or slightly off-white color, with colored spots. Discoloration may indicate inadequate storage or packaging conditions.

The MNP may slightly change the color shade of the food. Depending on the food to which the MNP is added, a change in the color shade is more or less visible. Iron-containing active ingredients, in particular, can discolor the food.

Examples:

- Vitamin B2 is a food colorant and may add a shade of yellow
- Fe-Fumarate colors in the form of violet spots
- The NaFeEDTA in tea turns it dark
- Fe-Pyrophosphate gives a slightly gray touch

Other colored particles are present, but hardly visible (e.g. copper salts, vitamin B12, folic acid, vitamin A)

Depending on the formulation, it may be feasible to include a respective comment on the label or the consumer information.

6.2.2.6 Allergens

If a raw material is used that might contain a potential allergen (e.g. soyprotein), this must be stated in the list of ingredients. The Codex General Standard for the Labelling of Prepackaged Foods[3] lists these potential allergens.

6.2.3 Overages

Adequate overages should be defined for the individual formulation, as the required overage mainly depends on the specific manufacturing (mainly humidity, temperature, and light exposure) and storage conditions. This section summarizes the general experience of premix manufacturers, and the specific requirements for individual formulations shall be verified by stability tests.

As a general rule, any adverse manufacturing conditions, which may contribute to the degradation of ingredients, should be avoided.

The adequate overages should be verified with the selected form of the active ingredient form, as there are substantial differences in the stability of different qualities and presentations of the active ingredients. The table below indicates suggested overages, which may be the basis for MNP development.

The ranges apply to MNPs packed in tight PET / Al / PE sachets (refer to Section 7.2.7). The lower overage in the table below may be applied to temperatures below 25°C and shelf-lives of 24 months; the higher overage may be applied to higher temperatures, e.g. tropical areas.

Adequate overages for specific manufacturing and storage conditions have to be identified during formulation development.

3. Codex Stan 1-1985; rev. 1-1991

Stability tests shall be performed to confirm the adequate overages (refer to Section 6.2.2.)

	Indicative overage %	
	Low	**High**
Vitamins		
Vitamin A	30	45
Vitamin D3	30	50
Vitamin E	10	15
Vitamin K1	30	50
Vitamin B1	25	40
Vitamin B2	25	45
Vitamin B6	25	30
Vitamin B12	25	35
Niacin	10	30
Folic acid	25	35
Vitamin C	15	30
Minerals*		
Iron	10	10
Zinc	10	10
Copper	10	20
Selenium	10	50
Iodine**	20	30

*For minerals, with the exception of iodine, overages are required to compensate for variation (refer to Section 6.2.2.3) to ensure compliance with the label claim; no compensation is required for changes in potency during storage.

** Overages for iodine are recommended due to a certain volatility of the substance.

Temperatures above 35°C should be avoided wherever possible, as it is difficult to predict the expected losses or to set standardized overages for these temperatures.

The most sensitive active ingredients and, usually, those that are limiting in terms of shelf life are vitamin A and vitamin D, but vitamins C, B1, and folic acid may also limit shelf-life.

Sensitivity and the subsequent likelihood of loss may vary substantially depending on chemical form, product form formulation, product form technology, the producer of the active ingredient, etc.

6.2.4 Shelf-Life Studies and Stability Data

The manufacturer shall conduct a shelf-life study for each MNP. These stability data should cover the entire shelf-life. The batches used for the shelf-life study should be manufactured under standard manufacturing conditions and starting materials (raw materials and packaging materials) intended for use for commercial manufacturing shall be used.

The product should be stored in controlled temperature and humidity conditions. Generally accepted conditions are:

- 25°C ± 2°C/60% ± 5% RH

or

- 30°C ± 2°C/65% ± 5% RH

Accelerated stability testing conditions may be considered as a rapid test method to compare qualities of different MNP finished product formulations. However, stability results obtained under these conditions should only be used as supporting data, and not as a reliable method to predict MNP quality under normal storage conditions.

- 40°C ± 2°C/75% ± 5% RH

At each testing interval, the entire specification should be tested. When defining the specification limits, it should be considered that, for certain parameters, degradation may take place. Thus, their content at the beginning of the shelf life must be higher than the label claim, in order to ensure that the specification limits are still met at the end of the MNP's shelf life.

6.2.5 Label Declaration

In essence, the declaration must follow country-specific requirements. In the absence of country specific regulations, the Codex Alimentarius labeling requirements must be obeyed. "Food labeling" 5th edition by WHO/FAO 2007 should be used as a reference.

The declaration may have to be stated on different printed packaging components, such as cardboard boxes, sachets, package unit labels, and leaflets (consumer information / package inserts).

General Requirements

The MNP Finished Product (in general, the cardboard box) shall contain relevant information, such as the:

- product name
- number of servings/sachets
- composition
- manufacturer, including address
- information about target users
- dosage information
- batch number
- expiry date
- storage conditions, and
- further information, due to regulatory requirements.

This information should be provided on the outer package, which is, in general, a cardboard box. The MNP sachets should contain, at minimum:

- the product name
- information about target users
- dosage information, and
- the expiry date.

It may be useful to indicate on the MNP sachet that the individual sachet is part of a larger package, and that further information may be found on this package.

Transport cartons, which contain several units of MNP Finished Product, should be adequately labeled, and should contain at least the following information:

- the product name
- the manufacturer, including address
- the batch number
- the expiry date
- storage conditions, and
- the number of units contained in the transport carton.

Contents of Active Ingredients

The declaration of the contents of active ingredients should be carried out in the following units, unless different requirements are defined in local regulations:

Active Ingredient	Reference Substance	Unit
Vitamin A	Retinol	µg RE / IU
Vitamin D3	Cholecalciferol	µg / IU
Vitamin E	d-α-Tocopherol	mg TE
Vitamin K1	n/a	µg
Vitamin B1	Thiamin	mg
Vitamin B2	Riboflavin	mg
Vitamin B6	Pyridoxine	mg
Niacinamide	n/a	mg
Folic acid	n/a	mg or µg
Pantothenic acid	n/a	mg
Vitamin B12	Cobalamin	µg
Vitamin C	Ascorbic acid	mg
Iron	n/a	mg
Zinc	n/a	mg
Copper	n/a	mg
Selenium	n/a	µg
Iodine	n/a	µg

Dosage

As regards any information on reference values (e.g. Recommended Daily Allowance (RDA), Recommended Nutrient Intake (RNI), or Nutrient Reference Value (NRV)), the source of the reference values should be mentioned, as these values may vary from country to country, and are rarely harmonized.

The following reference values are suggested:

- single servings: the reference values per micronutrient per serving, and
- multiple servings: either the amount per individual serving or the number of servings per packaging unit.

List of ingredients

Information should be provided about all of the ingredients being used in the formulation (active ingredients and excipients). In general, the list should be written in the order of the amount of the ingredient included in the formulation, i.e. the ingredient which comes in the highest amount should be mentioned first and the ingredient in the lowest amount should be mentioned last.

Information should be provided about those allergens which are potentially included (refer to Section 6.2.2.6).

Target Groups

The target group shall be mentioned on the label.

Further relevant information

The product name, and the name and address of the manufacturer, as well as variable data (including the batch number, expiry or "best-before" date, and – as locally required – the manufacturing date) is further information to be declared in product labeling.

Where the MNP may cause food discoloration, it may be useful to include respective information for the consumers.

Users may be advised not to dispose of empty sachets into the environment.

6.3 Starting Material

The quality of each starting material shall be known prior to its use in manufacturing.

Raw material and primary packaging material should comply with the requirements of Codex Alimentarius,[4] or compendial standards (where available) or should be of food grade quality, as outlined in the following sections.

Further requirements for starting material quality testing are outlined in Section 7.3.2.

4. Advisory Lists of Nutrient Compounds for Use in Foods for Special Dietary Uses intended for Infants and Young Children, CAC/GL 10-1979, Rev. 2009

6.3.1 Vitamins

6.3.1.1 Sensitivity of Micronutrients towards Different Impact Factors

When processing vitamins, their sensitivity towards different impact factors should be considered. The following table gives an overview of their sensitivity:

	Light	Oxidizing agents	Reducing agents	Heat	Humidity	Acids	Alkalis
Vitamin A	+++	+++	+	++	+	++	+
Vitamin D	+++	+++	+	++	+	++	++
Vitamin E	++	++	+	++	+	+	++
Vitamin K	+++	++	+	+	+	+	+++
Vitamin C	+	+++	+	++	++	++	+++
Thiamin B1	++	+	+	+++	++	+	+++
Riboflavin B2	+++	+	++	+	+	+	+++
Niacin	+	+	++	+	+	+	+
Vitamin B6	++	+	+	+	+	++	++
Vitamin B12	++	+	+++	+	++	+++	+++
Pantothenic Acid	+	+	+	++	++	+++	+++
Folic acid	++	+++	+++	+	+	++	++
Biotin	+	+	+	+	+	++	++

\+ = barely or not sensitive
++ = sensitive
+++ = highly sensitive

Source:
Sensitivity of Vitamins, DSM USAID Fortification Basics (Stability), 2012

In summary, the most sensitive nutrients in MNPs are:

- vitamin A, and
- vitamin D,

followed by the sensitive nutrients:

- vitamin C
- vitamin B1
- folic acid, and
- vitamin K1

The sensitivity of the micronutrients shall be considered when establishing overages (refer to Section 6.2.1).

6.3.1.2 General Remarks

The following sections provide information about vitamin and mineral forms as described in official monographs.

Commercially available substances may have activities and compositions which differ from the information contained in the monographs. Thus, the conversion factors given in the tables below refer to the chemical substances (vitamin or mineral form), and different conversion factors may have to be applied to the actual commercial product.

6.3.1.3 Vitamin A

Vitamin Forms	**Applicable Monographs** (examples)	**Conversion Factors (CF)** 1 µg Retinol x CF = µg Vitamin Form containing 1 µg Retinol
Retinyl acetate	EP, USP, FCC	1.147
Retinyl palmitate	EP, USP, FCC	1.832

1 µg RE (Retinol Equivalent) = 3.333 IU

Selection criteria:

- Vitamin A Palmitate 250,000 IU / g cold water dispersible, spray dried, stabilized, animal free (in case of low vitamin A content e.g. 100 µg/g).
- Vitamin A Palmitate 250,000 IU/g cold water dispersible, beadlets, stabilized, animal free (for high potency products only e.g. 400 µg/g).
- Vitamin A Acetate 250,000 IU/g cold water dispersible, beadlets, stabilized, animal free (for high potency products only).
- Vitamin A Acetate 325,000 IU/g cold water dispersible, beadlets, stabilized, animal free (for high potency products only).

6.3.1.4 Vitamin D

Vitamin Forms	**Applicable Monographs** (examples)	**Conversion Factors**
Cholecalciferol (D3)	EP, USP, FCC	1 µg = 40 IU
Ergocalciferol (D2)	EP, USP, FCC	1 µg = 40 IU

Selection criteria:

- vitamin D3 100,000 IU/g cold water dispersible beadlets or spray dried, stabilized, and
- vitamin D2 100,000 IU/g beadlets or spray dried, stabilized, (used in cases, where non-animal origin is required).

6.3.1.5 Vitamin E

Vitamin Forms	**Applicable Monographs** (examples)	**Conversion Factors (CF)** 1 mg TE x CF = mg Vitamin Form containing 1 mg TE
D-alpha-Tocopheryl acetate	EP, USP, FCC	1.1
DL-alpha-Tocopheryl acetate	EP, USP, FCC	1.49

Selection criteria:

- Vitamin E 50% cold water dispersible, spray dried (either DL-alpha-Tocopheryl acetate or D-alpha-Tocopheryl acetate).

6.3.1.6 Vitamin K1

Vitamin Forms	**Applicable Monographs** (examples)	**Conversion Factors (CF)**
Phytomenadione	EP, USP	n/a

Selection criteria:

- Vitamin K1 5% cold water dispersible, spray dried.

6.3.1.7 Vitamin C

Vitamin Forms	**Applicable Monographs** (examples)	**Conversion Factors** 1 mg Ascorbic Acid x CF = mg Vitamin Form containing 1 mg Ascorbic Acid
L-Ascorbic acid	EP, USP, FCC	1
Sodium-L-ascorbate	EP, USP, FCC	1.125
Calcium-L-ascorbate x $2H_2O$	EP, USP, FCC	1.211

Selection criteria:

- L-Ascorbic acid and/or sodium or calcium-L-ascorbate, depending on acceptable acidity.

6.3.1.8 Vitamin B1 (Thiamin)

Vitamin Forms	**Applicable Monographs** (examples)	**Conversion Factors** 1 mg Thiamin x CF = mg Vitamin Form containing 1 mg Thiamin
Thiamin hydrochloride	EP, USP, FCC	1.1212 – 1.338
Thiamin mononitrate	EP, USP, FCC	1.2337

Selection criteria:

- Thiamine mononitrate is less hygroscopic than hydrochloride.

6.3.1.9 Vitamin B2 (Riboflavin)

Vitamin Forms	**Applicable Monographs** (examples)	**Conversion Factors (CF)** 1 mg Riboflavin x CF = mg Vitamin Form containing 1 mg Riboflavin
Riboflavin	EP, USP, FCC	1
Riboflavin-5'-phosphate Sodium	EP, USP	1.2709
Riboflavin-5'-phos-phate Sodi-um x $2H_2O$	USP	1.3667

Selection criteria:

- Riboflavin (yellow) or Riboflavin-5'phosphate Sodium (greenish yellow).

6.3.1.10 Vitamin B6 (Pyridoxine)

Vitamin Forms	**Applicable Monographs** (examples)	**Conversion Factors (CF)** 1 mg Pyridoxine x CF = mg Vitamin Form containing 1 mg Pyridoxine
Pyridoxine hydrochloride	EP, USP, FCC	1.2155

Selection criteria: n/a

6.3.1.11 Vitamin B12

Vitamin Forms	**Applicable Monographs** (examples)	**Conversion Factors (CF)** 1 µg Cobalamin x CF = µg Vitamin Form containing 1 µg Cobalamin
Cyanocobalamin	EP, USP, FCC	1.0196
Hydroxocobalamin	EP, USP	1.0128

Selection criteria:

- Vitamin B12 1% or 0,1% spray dried, stabilized, with 100% loaded particles.

6.3.1.12 Pantothenic Acid

Vitamin Forms	**Applicable Monographs** (examples)	**Conversion Factors (CF)** 1 mg Pantothenic Acid x CF = mg Vitamin Form containing 1 mg Pantothenic Acid
Calcium-D-pantothenate	EP, USP, FCC	1.0878

Selection criteria: n/a

6.3.1.13 Folic Acid

Vitamin Forms	**Applicable Monographs** (examples)	**Conversion Factors**
Folic acid	EP, USP, FCC	n/a

Selection criteria:

- Folic acid, preferably as 10% trituration.

6.3.1.14 Biotin

Vitamin Forms	**Applicable Monographs** (examples)	**Conversion Factors**
Biotin	EP, USP, FCC	n/a

Selection criteria:

- Biotin, pure or as 1% or 10% trituration.

6.3.2 Minerals

6.3.2.1 Iron (Fe)

Chemical Substance	**Applicable Monographs** (examples)	**Conversion Factors (CF)** 1 mg Fe x CF = mg Chemical Substance containing 1 mg Fe
Ferrous fumarate	EP, USP, FCC	3.0421
Ferrous fumarate, coated 60%	n/a	5.0701
Ferric pyrophosphate	FCC	4.1667
NaFeEDTA	FCC	7.5355
Ferrous bisglycinate	JECFA	Individual calculation required
Ferrous lactate	FCC	Individual calculation required

Selection criteria:

- Ferrous fumarate: uncoated at low concentrations, or coated in higher concentrations.
- Ferric pyrophosphate: micronized; mean particle size 3 µm; to ensure high bioavailability.
- NaFeEDTA: consider intake limits for EDTA set by JECFA[5] (iron intake via NaFeEDTA: 0.37 mg / kg body weight[6]; translates to 2.5 mg iron (from NaFeEDTA) / day for a 7 kg infant)
- As regards NaFeEDTA, ferrous bisglycinate, and ferrous lactate, there is currently evidence that these substances meet the criteria for bioavailability, minimal effect on the taste or color of the food it is mixed with, and minimal or no interaction with other micronutrients.[7]

6.3.2.2 Zinc (Zn)

Chemical Substance	**Applicable Monographs** (examples)	**Conversion Factors (CF)** 1 mg Zn x CF = mg Chemical Substance containing 1 mg Zn
Zinc oxide	EP, USP, FCC	1.2449
Zinc gluconate	USP, FCC	6.9097
Zinc sulphate x H_2O	EP, USP, FCC	2.7455
Zinc sulphate x 6 H_2O		4.1221
Zinc sulphate x 7 H_2O		4.3974

5. WHO Technical Report Series No. 947, Evaluation of certain food additives and contaminants, 2007.
6. Wreesmann CTJ. Reasons for raising the maximum acceptable daily intake (ADI) of EDTA and the benefits for iron fortification of foods for children
6 – 24 months of age. Maternal and Child Nutrition, DOI: 10.111/mcn.12110.
7. Home Fortification Technical Advisory Group. Manual on Micronutrient Powder (MNPs) Composition. Geneva: Home Fortification Technical Advisory Group, 2013.

Selection criteria:

- Zinc oxide has a mostly bland taste.
- The bioavailability of different zinc compounds is comparable.

6.3.2.3 Copper (Cu)

Chemical Substance	**Applicable Monographs** (examples)	**Conversion Factors** 1 mg Cu x CF = mg Chemical Substance containing 1 mg Cu
Copper Sulfate anhydrous	EP, USP, FCC	2.5116
Copper sulfate x 5 H_2O		3.9292
Copper Gluconate	USP, FCC	7.1408

Selection criteria: n/a

6.3.2.4 Selenium (Se)

Chemical Substance	**Applicable Monographs** (examples)	**Conversion Factors** 1 µg Se x CF = µg Chemical Substance containing 1 µg Se
Sodium Selenite	EP, USP	2.1902
Sodium selenite x 5 H_2O		3.3308

Selection criteria: n/a

6.3.2.5 Iodine (I)

Chemical Substance	**Applicable Monographs** (examples)	**Conversion Factors** 1 µg I x CF = µg Chemical Substance containing 1 µg I
Potassium Iodide	EP, USP, FCC	1.3081

Selection criteria: n/a

6.3.3 Excipients

6.3.3.1 Carriers

The currently used and most common carriers are listed below. Other carriers, e.g. starches and flours, might be considered as well, depending on the intended use, local customs, costs, and needs.

As carriers form the major part of the MNP formulation, low water content is a mandatory requirement, as water activity has a negative impact on the microbiological properties and stability of some micronutrients and, thus, on the shelf-life of the product. Furthermore, water content may cause discoloration.

Maltodextrin (e.g. EP, USP):

The best results are achieved with powdered maltodextrin, preferably with low DE values (e.g. 9-11). The product combines low hygroscopic properties, low sweetness, and low water content. Granulated maltodextrins are less recommended, as the particle size of these products is too high and may lead to de-mixing.

Other food source carriers

Rice or other cereal flour, starches, as well as soybean protein isolate, full fat soybean flour or milk/whey powder may be suitable as carriers. Particular attention has to be paid to the microbiological purity of these products.

For milk derived carriers, the absence of *Chronobacter sakazakii* has to be ensured, as this microorganism may cause fatal diseases.

6.3.3.2 Processing Aids

Processing aids are added for technological purposes, such as the improvement of mixing properties and flow rate, as well as for the prevention of caking (anti-caking agents).

Widely used substances:

Silicon dioxide (e.g. EP, USP):

Silicon dioxide improves flow rate, dosing and mixing properties, prohibits caking of the mix, and absorbs liquids.

The particle size should be ≤ 10 µm

Recommended dosage: 0.5 – 2%.

Tri calcium phosphate (e.g. EP, USP):

Tri calcium phosphate acts as an anti-caking agent.

The particle size should be ≤ 10 µm

Recommended dosage: 0.5 – 2%

6.3.4 Primary Packaging Material

Primary packaging material should adequately protect the MNP sachet content from moisture and light.

Currently, laminate foil is recommended for MNP Sachets. Such foil may have the following composition: PET/Al/PE, and more specifically PET 12/Al8/PE45. Alternative materials, e.g. foils such as Paper/Al/PE, have been tested and often performed inadequately.

It is acknowledged that laminate foil has a negative environmental impact, because neither is it bio-degradable nor can it be recycled, repurposed, or burnt. Hence, research is ongoing to develop alternative, more environmentally friendly materials.

Tests have to be performed by the manufacturer in order to prove the adequacy of any primary packaging material.

The table below shows an example of the specification of a laminate foil that has been proven adequate for MNP sachets.

Parameter	Requirement	Test Method
Weight	88±5 g/m²	ISO 536
Thickness	71±5 µm	ISO 1923
WVTR (Water Vapor Transmission) (37.8°C, % 90 RH, 1 atm)	<1 g/m²/day	ASTM E 96
OTR (Oxygen transmission) (23°C, %0 RH, 1 atm)	<5 cc/m²/day	ASTM D3985
Residual Solvents	<20 mg/m²	ASTM F 1884
Heat Seal Strength (125°C/14.7psi/1s)	Complies	ASTM F 2029
Lamination Strength	150g/25mm	ASTM F 904
Coefficient of Friction (COF)	<0.45	ASTM D 1894
Hygiene	Clean	Merck Hi-rise Color Test

cc = cubic centimeters (mL)

The information to be printed on the MNP sachets is specified in Section 6.2.3.

6.3.5 Secondary Packaging Material

Secondary packaging material does not have direct contact with the product, and thus the manufacturer has a certain flexibility when selecting it.

In general, MNP sachets are packaged in cardboard boxes, and the cardboard boxes are packaged in transport cartons. Both should protect the goods sufficiently, i.e. they should provide adequate stacking crush pressure stability. In order to define the stability, the humidity and temperature of the storage environment should be considered.

To provide adequate stability, transport cartons may be used which are made of corrugated carton or double-flute cartons.

Cardboard material shall be clean and odorless.

Packaging alternatives, e.g. pouches, may be considered in place of cardboard boxes.

Leaflets featuring instructions for consumers should be added, unless all instructions are printed on the cardboard box or the MNP sachet.

Common sales unit sizes are 30 MNP sachets per cardboard box, i.e. the quantity for one month, or two months in cases where dosage takes place every other day.

The information to be printed on the cardboard box, package insert, and transport carton is specified in Section 6.2.3.

7. MNP Production

7.1 Equipment and Facilities

7.1.1 Manufacturing Equipment

All equipment should be suitably for its intended purpose, which should be demonstrated by qualification (refer to Section 5.7.6.1).

Product contact parts and surfaces should be made of adequate material to avoid any negative impact on the MNPs, i.e. surfaces should be smooth, without crevices, and avoid abrasion. Lubricants or other material with a potential negative impact on product quality should be avoided. If possible, dedicated equipment should be used in order to exclude the risk of cross-contamination with other products being manufactured on the equipment.

After cleaning and before its use in the manufacturing process, the equipment must be dry in order to prevent the formation of mold.

The design and positioning of the equipment should allow easy access for cleaning and servicing, and shall provide adequate protection for the operators when they use the equipment.

Examples for operator safety and protection:

- adequate electrical installations and explosion protection where required
- machine guarding, and
- protection from falls.

Logbooks should be available for each piece or group of equipment.

7.1.2 Room Conditions and Work-Flow

Rooms should be arranged so that they allow workflow in the process order, and minimize the crossing of material and personnel flows.

Facilities shall be designed to operate at an adequate temperature and low humidity. In particular, humidity must be kept at a low level, as it may promote the molding of the product and ingredients.

Sufficient workspace should be provided to allow all operations to take place under appropriate hygienic conditions and to provide a safe environment for the operators.

Examples for operator safety:

- non-slippery floors
- dust exhausts
- adequate clothing (also refer to Section 5.8.1.3)
- sufficient space and devices to allow tidy operations
- emergency exists

Rooms for different manufacturing operations should be separated. Thus, there should be areas for:

- weighing
- mixing/blending and bulk packaging
- intermediate storage and staging
- sachet filling
- final packaging, and
- equipment cleaning.

For more details on the design and equipment of rooms to allow work under hygienic conditions, refer to Sections 5.8.1.1 and 5.8.1.2.

7.1.3 Media

7.1.3.1 Water

As regards MNP manufacturing, water is solely used for cleaning purposes, and only potable water or higher purity water shall be employed.

The water quality should be as specified in the latest edition of the WHO Guidelines for Drinking Water Quality, or a higher standard.

Non-potable water, which may be used, for example, for fire control, or for other purposes without contact with the product or product-contact areas, shall have a separate system, which shall be identified and not be connected with nor allow reflux into the water system used for cleaning purposes.

7.1.3.2 Steam

For microbiological decontamination purposes, or for cleaning operations where high temperatures are required, steam may be used in MNP manufacturing. Such steam may only be generated from potable water or higher purity water.

7.1.3.3 Gases

Where gases are used, e.g. nitrogen or compressed air, and where such gases come into contact with the product, the quality should be specified and the supply network should avoid any contamination. Specific focus should be on potential contamination by oil.

7.2 MNP Manufacturing

7.2.1 Process Flow

As there are commercially available MNP pre-mix-concentrates and ready-to-fill MNP bulk, the manufacturer can start at different levels of vertical ranges of manufacturing:

Option 1: Manufacture of MNP powder by mixing the individual ingredients.

Option 2: MNP Pre-Mix Concentrates and addition excipients for dilution.

Option 3: Ready-to-fill MNP bulk.

The manufacturing processes follow the flow shown in Diagram 5.

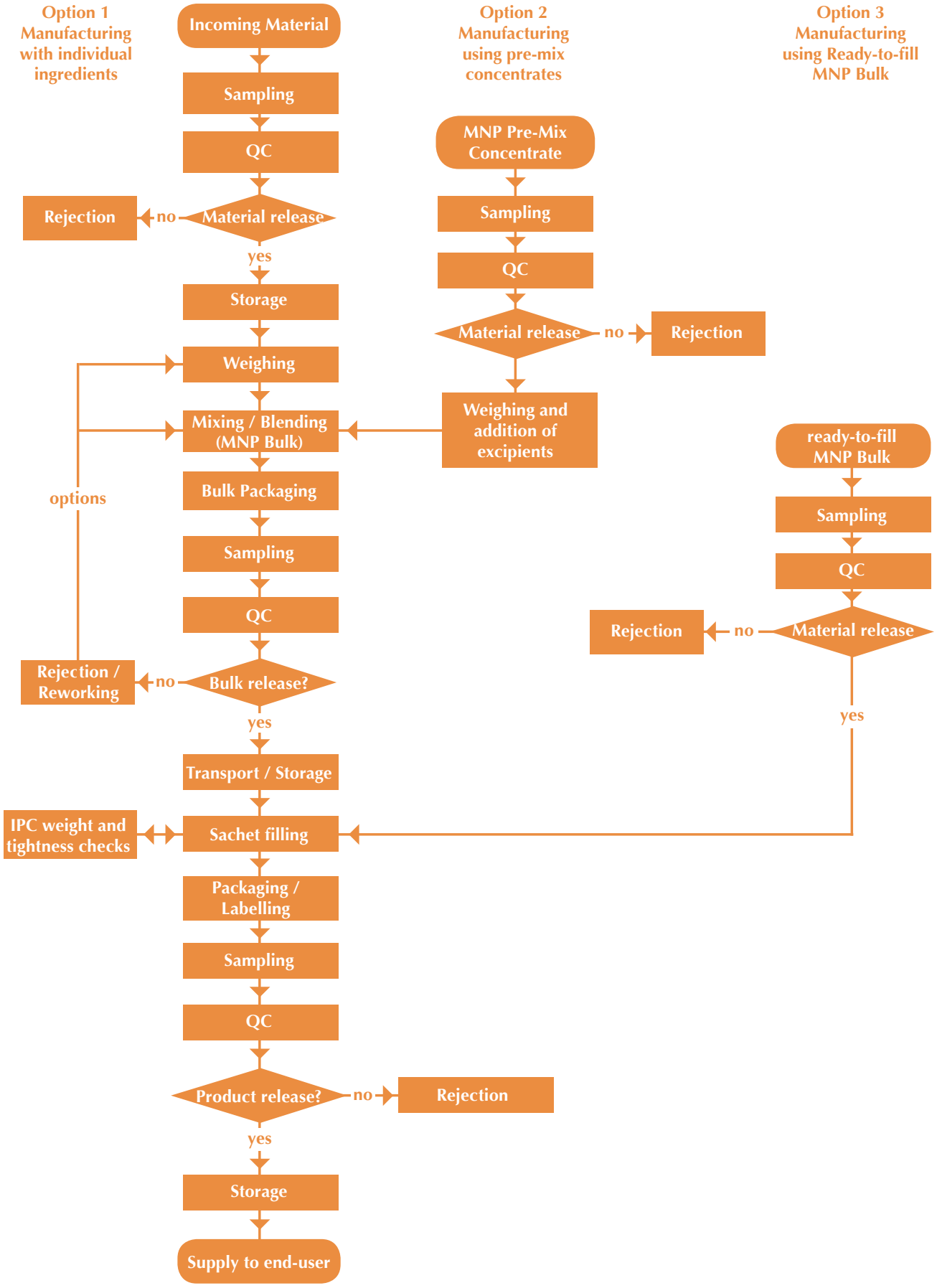


Diagram 5: Process-Flow for Different MNP Manufacturing Processes

7.2.2 Manufacturing Instructions

Manufacturing instructions shall be in place for each product, as well as instructions on the use of the respective equipment.

Master production documents should contain instructions and information to follow, and shall have sufficient space for the respective entries. Major aspects include:

- the product name, code and number to allow unequivocal identification
- the batch number (this shall be entered for the current batch)
- the date and time of production (this shall be entered for the current batch)
- the equipment to be used, i.e. a clear indication of which equipment is being used
- the batch size
- the starting materials to be used:
    - the name of the material
    - the product code
    - the quantity to be used for the batch
- in chronological order, a detailed description of all manufacturing steps to be performed, and space for records (confirmation that the step has been performed, actual parameters, time, etc.)
- instructions on in-process-controls which must be performed, and space to record the results
- the target yield and space to enter the actual yield
- the packaging material to be used:
- the name of the material
- the product code
- the quantity
- a reconciliation of the printed packaging material
- examples of labels (with space to attach the label(s) from the actual batch) with the actual batch number, expiry date and, as required, manufacturing date

Space should be provided so that remarks and potential deviations can be noted.

Instructions should be given on print-outs or other records to be added to the documentation.

The manufacture of each batch shall be documented in the batch-specific manufacturing instruction.

7.2.3 Weighing

Weighing should be carried out on calibrated balances in areas which are adequately clean, in order to avoid contamination.

Each raw material should be dosed into an individual container, i.e. material should not be added step-wise into one container. The individual containers should be identified with the raw material code, raw material batch number, and amount.

Once the operator has performed the weighing operations, the date on which the operation was performed shall be documented in the manufacturing record. A second operator should verify the weighing operation, and this verification should also be documented.

7.2.4 Mixing/Blending

In addition to the information about the equipment to be used, the manufacturing instructions should specify:

- the charging sequence of the ingredients in the premix, and
- a detailed description of the mixing operations for each step (e.g. mixing time, agitator type and speed).

The performance of the mixing process must be verified by a validation procedure, carried out with the specific formula under the specified mixing conditions.

7.2.5 Bulk Handling

MNP bulk may be packed into MNP sachets immediately after manufacturing. If the MNP bulk is not packaged immediately, it must be staged in the manufacturer's facilities or transported to external filling facilities, in situations where filling into sachets is performed as an outsourced activity.

In any event, it must be ascertained that storage and transport of MNP bulk material does not have any negative impact on the MNP powder's quality and homogeneity.

Thus, the MNP bulk must be protected from light, humidity, and high temperature, and any potential contamination. The containers must be identified with the:

- product name
- batch number, and
- manufacturing date.

The holding time (storage time and conditions) of the MNP bulk material shall be defined before it is filled into sachets.

7.2.6 Filling/Dosing

The following critical points in the packaging process must be considered:

- low humidity and temperature conditions (the exact criteria need to be defined for the specific process by the manufacturer)
- homogeneity, i.e. the risk of segregation during final packaging
- de-dusting
- filling weight, and
- sealing tightness.

Homogeneity must be optimized during the product formulation. Filling into sachets, especially when high speed filling machines are used, might have a negative impact on product homogeneity. The performance during packaging into the sachets must be verified by a validation procedure, which is carried out with the specific formula on a specific filling machine. Changes in carrier type or product forms, and major changes in composition require new validation.

Filling weight and accuracy must be validated, and criteria must be established when the filling mechanism has to be adjusted in order to guarantee the maximum deviation of the average from the declared weight of ± 5%, and the maximum deviation of a single sachet of ± 10%.

Sealing tightness must be verified by a suitable validation process (an instrumental random test).

Sachet coding must be performed. with relevant and mandatory information. Depending on the specific requirements, MNP sachets may have to be coded with:

- the batch number
- the manufacturing date
- the expiry date, and
- running number coding to ensure traceability.

Note: Relevant local requirements should be taken into account when designing packaging equipment!

7.2.7 Packaging and Labeling

The defined quantity of MNP sachets must be packaged into the secondary packing container; in general, these are cardboard boxes. The cardboard boxes shall be printed with batch-specific data, i.e. the batch number, expiry date, and – as required – manufacturing date. With regard to further information which is required on the packaging material, refer to Section 6.2.3.

The reconciliation of packaging material shall be performed, i.e. a cross-check of the units delivered to manufacturing, the quantity consumed for packaging, and the quantity returned to storage.

7.3 Quality Control

7.3.1 Instruments and Facilities

Quality control facilities should be separate from production facilities. The quality control area should be equipped with adequate instruments, and the instruments should be qualified (refer to Section 5.7.6.1).

A logbook should be in place for each instrument.

7.3.2 Quality Testing

7.3.2.1 Starting Materials

Starting materials should be handled according to the principles outlined in Section 5.7.4.

Information about the quality of the starting material is obtained either by quality control testing, or via supplier certificates. It should be defined in a procedure under which circumstances supplier certificates may be accepted instead of individual batch testing.

Sufficient and reliable information about the supplied quality should be available before renouncing internal testing. Spot-checks should be performed, although supplier certificates may be accepted.

When MNP premix is purchased for further processing, it is considered to be starting material and has to undergo quality testing. Test criteria should consider quality criteria which may have

changed during transportations and storage. For example, the decay of vitamins or microbial contamination may have occurred.

7.3.2.2 MNP Bulk

MNP bulk or ready-to-fill MNP bulk shall be quality tested before it is released for filling into sachets.

In-process-control testing may be required in order to control the manufacturing process.

7.3.2.3 MNP Sachets

Each batch of MNP sachets shall undergo testing for compliance with the specification. The specification shall include requirements related to chemical, physical, and microbiological testing.

7.3.3 Test Plans Starting Material

Test plans should follow the principles outlined in Section 5.7.7.5.

Depending on the criticality of the starting material, comprehensive test plans shall be in place. Active ingredients testing should, in general, be more extensive than testing for excipients; the testing of primary packaging material should be more extensive than the testing of secondary packaging material. (Remark: Depending on the type of secondary packaging material, secondary packaging may present an important moisture and oxygen barrier. Here, of course, the focus must be on the barrier properties of the secondary packaging material.)

Test plans should comprise all parameters defined in the specifications. If certain parameters are not tested in-house, but reference shall be made to data from supplier certificates, this may be carried out if the principles described in Section 5.7.3 are adhered to.

Starting material test plans should include a test parameter, which makes reference to successful checking of the incoming material as described in Section 5.7.8.

In general, the test plans for raw material should contain the parameters outlined in the respective monographs. Additional parameters, such as particle size distribution, may be of further importance.

For printed packaging material, which may be sachet foil, cardboard boxes, carton labels, or leaflets, testing the correctness of printed information is mandatory. There should be approved templates of the printed packaging material, and newly supplied batches of printed packaging material should be cross-checked for conformity with the respective template.

7.3.4 Test Plans MNPs

Test plans should follow the principles outlined in Section 5.7.7.5.

7.3.4.1 Chemical Parameters

The quantity and identity of the active ingredients shall be tested.

Example limit values are given in Section 6.2.1 for MNP powder and MNP sachets in the columns:

- minimum / maximum limit MNP powder
- minimum / maximum limit MNP sachet

Limit values shall be specified accordingly for any other formulation.

7.3.4.2 Physical Parameters

The following physical parameters should be tested:

- printing of variable data (batch number, expiry date and – optional – manufacturing date)
  - correctness of the information
    - legibility.
- Tightness of the MNP sachets (at the beginning, middle, and end of the batch). Tightness testing in quality control may be dispensable, if reliably controlled during manufacturing in in-process-controls.
- Sachet seal strength.

7.3.4.3 Microbiological Parameters

MNP sachets from the beginning and end of a batch shall be tested for their microbial load.

For validated and long-term established processes, microbiological testing may be reduced to a skip-lot testing, i.e. testing may not be performed on each batch.

Type of microorganism	Limit value
Total CFU (aerobic bacteria)[1]	Max. 1,000 CFU/g
Yeasts and molds[1]	Max. 100 CFU/g
Escherichia coli[1]	Negative in 10g
Salmonella spp.[1]	Negative in 50g
Staphylococcus aureus[1]	Negative in 10g
Chronobacter sakazakii[2]	Negative in 10g
Bacillus cereus[3]	Max. 10/g
S-reducing clostridia[3]	Max. 10/g
Enterobacteriaceae[3]	Negative in 10g
Pseudomonas aeruginosa[3]	Negative in 10g
Pseudomonas spp.[3]	Negative in 1g

[1)] UNICEF specification in the tender RFP-DAN-2014-501823

[2)] Limit value is relevant for MNPs with milk-based carriers (Commission Regulation (EC) No. 2073/2005, as at 1December 2011)

[3)] Further applicable criteria mentioned in other publications

7.3.5 Test Methods

7.3.5.1 Chemical

As far as possible or feasible, the test methods shall be taken from the official monographs, i.e. mainly pharmacopoeias.

Methods for vitamin analyses have been developed by active ingredient manufacturers. For instance, Sight and Life[8] provides analytical methods for vitamins on request.

7.3.5.2 Physical

For tightness testing of the sachets, a method for container closure integrity testing should be applied.

Different methods may be appropriate; two examples are given below.

A) Immerse the sachets in water, subject them to a controlled external pressure, and check for air bubbles, which indicate that sachets are not tight.

B) Sachets are submerged into a methylene blue solution in a desiccator, and exposed to the blue bath for a defined time. After this time, the sachets are washed to remove excessive blue color and dried afterwards. The dry sachets are opened, and it is visually checked if the blue color has intruded into the sachet. If there is no discoloration of the powder, the sachets comply with the tightness requirements.

Seal strength is another parameter which should be tested. Although seal strength is a prerequisite for tight sachets, seal strength alone does not necessarily indicate tightness: Individual seals may be strong, but sachets may still not be tight.

Seal strength is tested with a tensile test machine.

7.3.5.3 Microbiological

Adequate test methods for microbiological testing may be found in, for example, the European Pharmacopoeia (Sections 2.6.12 and 2.6.13), or the United States Pharmacopoeia.

7.3.6 Sampling

Sampling shall follow pre-defined sampling plans, and the sampling process shall be defined to avoid any contamination or other negative impact during the sampling process.

Clean equipment shall be provided for sampling; sterile equipment, likewise, for samples taken for microbiological testing.

Samples shall be taken under adequate protection, i.e. the opening of containers should be carried out in a way that contamination is prevented.

7.3.6.1 Starting Materials

Samples of raw materials and primary packaging materials shall be taken, which allow the verification of the identity and quality of the material.

Sampling should not be performed in open warehouse areas; however, separate sampling areas should be available.

For raw materials which are sensitive (e.g. oxygen or light sensitive), specific protections should be provided.

Units which have been opened for sampling should be identified, and the name of the person who carried out the sampling, as well as the date of the sampling, should be indicated. After sampling, containers should be adequately closed.

8. Sight and Life may be contacted via info@sightandlife.org

7.3.6.2 MNPs

Samples shall be taken at any step in the manufacturing process where quality testing needs to be performed.

The quantity of sampling points and sampling positions should be defined in a way that subsequent analytical testing provides an overview of the product quality. It may therefore be required that, for example, sampling points are defined at different levels in containers, or at different points in time during filling.

During MNP sachet filling, at a minimum samples should be taken at the beginning, middle and end of the filling process.

7.3.7 Retention Samples

Retention samples shall be kept for all

- raw material batches
- primary packaging material batches, and
- MNP batches.

The quantity of the retention samples should be sufficient to allow two complete analyses according to the specification.

Retention samples of raw materials should be kept in adequate containers, which do not compromise the quality.

MNP finished product retention samples shall be sales units.

Retention samples shall be properly identified and stored under adequate conditions. The storage time for reference samples should be shelf life + 12 months.

Access should be possible within a short space of time; in general, one day is considered to be suitable.

7.3.8 Example Certificate of Analysis (CoA)

A certificate should be issued for each batch of MNP. The table below gives an example of the content of such certificate. Additional parameters may be relevant to certify adequate product quality.

Certificate of Analysis			
Product Name: *XXX*		**Batch-No.: *XXX***	
Parameter	**Requirements / Tolerances**	**Unit**	**Result***
Chemical and Physical			
Appearance	Fine granular powder	n/a	*Complies*
Color	Grayish yellow	n/a	*Complies*
Tightness of sachet	Tight	n/a	*Complies*
Moisture	4.0 – 5.0	%	*4.2*
Vitamin A	360 - 667	µg RE	*454*
Vitamin D3	4.5 - 8.63	µg	*6.8*
Vitamin E	4.5 - 6.16	mg TE	*5.35*
Vitamin B1	0.45 - 0.77	mg	*0.62*
Vitamin B2	0.45 - 0.834	mg	*0.72*
Vitamin B6	0.45 - 0.715	mg	*0.57*
Folic Acid	81 - 140	µg	*124*
Vitamin B12	0.81 - 1.40	µg	*1.18*
Vitamin C	27 - 38	mg	*34.3*
Niacin	5.4 - 8.58	mg	*7.1*
Iron	9 - 12.1	mg	*11.9*
Zinc	3.69 - 4.96	mg	*4.46*
Copper	0.504 - 0.739	mg	*0.68*
Selenium	15.3 - 30.6	µg	*29.4*
Iodine	72 - 140.4	µg	*113*
Microbiology			
Total CFU (aerobic bacteria)	Max. 1,000	CFU / g	*<10*
Yeasts and molds	Max. 100	CFU / g	*<10*
Escherichia coli	Negative in 10 g		*Not detected*
Staphylococcus aureus	Negative in 10 g		*Not detected*
Salmonella spp.	Negative in 50 g		*Not detected*

This is to certify that the sample has been tested by the Quality Control Department and was found to meet the specification

_____ _____

(Signature of Head of QC) *(Date)*

* Results are examples only

7.4 Material Storage

7.4.1 Stock Rotation

Starting material should be consumed following the FEFO-principle (first expiry, first out); i.e. material with the shortest shelf-life (FE = first expiry) shall be consumed first (FO = first out).

MNP finished product should be delivered based on the FIFO-principle (first in, first out); i.e. product should leave the warehouse following the order of manufacture.

As a general rule, purchased or produced quantities should allow consumption in due time, i.e. there should not be excessive stock of any material, in order to avoid a situation whereby such material on stock comes close to the end of its shelf-life before it is consumed.

7.4.2 Storage Conditions

Storage conditions (temperature and humidity) should be in compliance with:

- the suppliers' recommendations for starting material, and
- the conditions of the stability studies for MNP sachets, 25°C or 30°C and humidity below 60/65 % RH (refer to Section 6.2.2).

Storage conditions should be monitored and recorded.

8. Further Reading

1. Joint statement by WHO/UNICEF/WFP, 2007: "Preventing and controlling micronutrient deficiencies in populations affected by an emergency: Multiple Vitamin and mineral supplements in pregnant and lactating women and for children aged 6 – 59 months"
2. GAMPÒ 5: A Risk-Based Approach to Compliant GxP Computerized Systems; ISPE February 2008
3. ICH Harmonised Tripartite Guideline; Validation of Analytical Procedures: Text and Methodology Q2(R1), November 2005
4. The Potential of Encapsulated Iron Compounds in Food Fortification: A Review, Michael B. Zimmermann, Int. J. Vitam. Nutr. Res., 74 (6), 2004, 453–461
5. Nutrition Unit Code of practice for food premix operations, Pan American Health Organization. Family and Community Health Area, Washington, D.C: PAHO, © 2005. FCH/NU/66-16/04; ISBN 92 75 12589 9
6. EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines, Annex 15 "Qualification and Validation"
7. Commission Regulation (EC) No 2073/2005, including all current amendments
8. Food safety management systems – Requirements for any organization in the food chain (ISO 22000:2005)
9. Home Fortification Technical Advisory Group. Manual on Micronutrient Powder (MNPs) Composition. Geneva: Home Fortification Technical Advisory Group, 2013
10. Codex Alimentarius: Hazard Analysis and Critical Control Point System and Guidelines for its application, Annex to CAC/RCP 1-1969 (Rev. 4-2003)
11. Codex Alimentarius: Advisory Lists of Nutrient Compounds for Use in Foods for Special Dietary Uses intended for Infants and Young Children, CAC/GL 10-1979, Rev. 2009
12. "Food labeling" 5th edition by WHO/FAO 2007
13. WHO Technical Report Series No. 947, Evaluation of certain food additives and contaminants, 2007
14. Wreesmann CTJ. Reasons for raising the maximum acceptable daily intake (ADI) of EDTA and the benefits for iron fortification of foods for children 6 – 24 months of age. Maternal and Child Nutrition, DOI: 10.111/mcn.12110

Appendix 1 – Example Specification

Specification	
Product	**Ascorbic Acid Fine Powder**
Technical Information	
Description	Ascorbic Acid Fine Powder is a practically odorless powder with a strong acid taste. It melts at about 190°C with decomposition.
Chemical names	L-threo-hex-2-enoic acid -lactone; 3-oxo-L-gulofuranolactone (enol form) Synonyms: L-ascorbic acid; L-*xylo*-ascorbic acid; L-(+)-ascorbic acid; vitamin C
CAS No.	50-81-7 HO
E No.	E 300
Formula	$C_6H_8O_6$
Molecular mass	176.13 g/mol
Product Properties	
Appearance	Powder
Color	White to slightly yellow
Assay	99.0 -100.5%
Fineness (US standard sieves): through sieve No. 100	Min. 90%
Solution 5% in water:	Clear and colorless
Solubility	Freely soluble in water (approx. 30 g per 100 mL), sparingly soluble in alcohol (approx. 2 g per 100 mL), and practically insoluble in ether, petroleum ether, chloroform, oils and fats.
pH (c = 5 in water)	2.2 – 2.5
Identity	Complies
Specific rotation (589 nm, 20°C, c = 10 in water)	+20.5° to 21.5°
Loss on drying	Max. 0.1%
Related substances	
D-sorbosonic acid (impurity C)	Max. 0.15%
Methyl D-sorbosonate (impurity D)	Max. 0.15%
Unspecified impurities (each)	Max. 0.10%
Total (other than C and D) *	Max.0.2%
*Disregard limit	0.05%
Sulphated ash (Residue on ingnition)	Max. 0.1%
Heavy metals	Max. 10 ppm
Lead	Max. 2 ppm
Mercury	Max. 1 ppm
Zinc	Max. 25 ppm
Copper	Max. 5 ppm
Iron	Max. 2 ppm
Arsenic	Max. 3 ppm
Oxalic Acid (Impurity E)	Max. 0.2%
Residual Solvents	
Ethanol	Max. 1000 mg/kg
Methanol	Max. 3000 mg/kg
Further information and requirements	

Specification	
Shelf-life	The product may be stored for 36 months from the date of manufacture in the unopened original container and at a temperature below 25°C..
Storage	Protect from humidity and light and store below 25°C.
Safety	Avoid ingestion, inhalation of dust or direct contact by applying suitable protective measures and personal hygiene. For full safety information and necessary precautions, please refer to the respective Material Safety Data Sheet.
Uses	For the enrichment, standardization or stabilization of dry food preparations and drinks; for the improvement of the baking qualities of flour; as an agent in dry mixes for curing meat.
Compliance Information	Halal, kosher.
Packaging	Shipping containers shall be impervious to light, contain a suitable moisture barrier, and be sealed and tamper evident.
Lot Identification	All shipping containers shall be clearly marked with the product name, manufacturer, manufacturer's address, lot number, and date of manufacture.
Certification	The vendor shall supply a certificate of analysis documenting conformance to specification for all lots prior to or at the time of delivery.

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