INTERNATIONAL STANDARD

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Primary packaging materials for medicinal products — Particular requirements for the application of ISO 9001:2008, with reference to Good Manufacturing Practice (GMP)

Articles de conditionnement primaire pour médicaments — Exigences particulières pour l'application de l'ISO 9001:2008 prenant en considération les Bonnes Pratiques de Fabrication (BPF)

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 15378 was prepared by Technical Committee ISO/TC 76, *Transfusion, infusion and injection, and blood processing equipment for medical and pharmaceutical use.*

This second edition cancels and replaces the first edition (ISO 15378:2006), which has undergone a minor revision to adapt this International Standard to ISO 9001:2008 and update references.

Introduction

0.1 General

This International Standard identifies Good Manufacturing Practice (GMP) principles and specifies requirements for a quality management system applicable to primary packaging materials for medicinal products. The realization of GMP principles in production and control of primary packaging materials within organizations is of great importance for the safety of a patient using the medicinal product, because of their direct product contact. The application of GMP for pharmaceutical packaging materials helps ensure that these materials meet the needs and requirements of the pharmaceutical industry.

This International Standard is an application standard for primary packaging materials, which contains the normative text of ISO 9001:2008.

The conventions for the layout of this International Standard are the following.

— *Those clauses or subclauses that are quoted directly and unchanged from ISO 9001:2008 are in boxed text.*

— *Texts in italics contain additional relevant GMP information regarding primary packaging materials.*

GMP terms and definitions are included in Clause 3. If listed, the source is referred to in brackets.

ISO 9001:2008, Quality management systems — Requirements

0.1 General

The adoption of a quality management system should be a strategic decision of an organization. The design and implementation of an organization's quality management system is influenced by

a) its organizational environment, changes in that environment, and the risks associated with that environment,

b) its varying needs,

c) its particular objectives,

d) the products it provides,

e) the processes it employs,

f) its size and organizational structure.

It is not the intent of this International Standard to imply uniformity in the structure of quality management systems or uniformity of documentation.

The quality management system requirements specified in this International Standard are complementary to requirements for products. Information marked "NOTE" is for guidance in understanding or clarifying the associated requirement.

This International Standard can be used by internal and external parties, including certification bodies, to assess the organization's ability to meet customer, statutory and regulatory requirements applicable to the product, and the organization's own requirements.

The quality management principles stated in ISO 9000 and ISO 9004 have been taken into consideration during the development of this International Standard.

A key objective of this International Standard is to define harmonized primary packaging material requirements. It includes some particular requirements for primary packaging materials, which are derived from Good Manufacturing Practices for the production, control, etc. of medicinal products.

0.2 Process approach

ISO 9001:2008, Quality management systems — Requirements

0.2 Process approach

This International Standard promotes the adoption of a process approach when developing, implementing and improving the effectiveness of a quality management system, to enhance customer satisfaction by meeting customer requirements.

For an organization to function effectively, it has to determine and manage numerous linked activities. An activity or set of activities using resources, and managed in order to enable the transformation of inputs into outputs, can be considered a process. Often the output from one process directly forms the input to the next.

The application of a system of processes within an organization, together with the identification and interactions of these processes, and their management to produce the desired outcome, can be referred to as the “process approach”.

An advantage of the process approach is the ongoing control that it provides over the linkage between the individual processes within the system of processes, as well as over their combination and interaction.

When used within a quality management system, such an approach emphasizes the importance of

a) understanding and meeting requirements,

b) the need to consider processes in terms of added value,

c) obtaining results of process performance and effectiveness, and

d) continual improvement of processes based on objective measurement.

The model of a process-based quality management system shown in Figure 1 illustrates the process linkages presented in Clauses 4 to 8. This illustration shows that customers play a significant role in defining requirements as inputs. Monitoring of customer satisfaction requires the evaluation of information relating to customer perception as to whether the organization has met the customer requirements. The model shown in Figure 1 covers all the requirements of this International Standard, but does not show processes at a detailed level.

NOTE In addition, the methodology known as “Plan-Do-Check-Act” (PDCA) can be applied to all processes. PDCA can be briefly described as follows.

Plan: establish the objectives and processes necessary to deliver results in accordance with customer requirements and the organization's policies.

Do: implement the processes.

Check: monitor and measure processes and product against policies, objectives and requirements for the product and report the results.

Act: take actions to continually improve process performance.

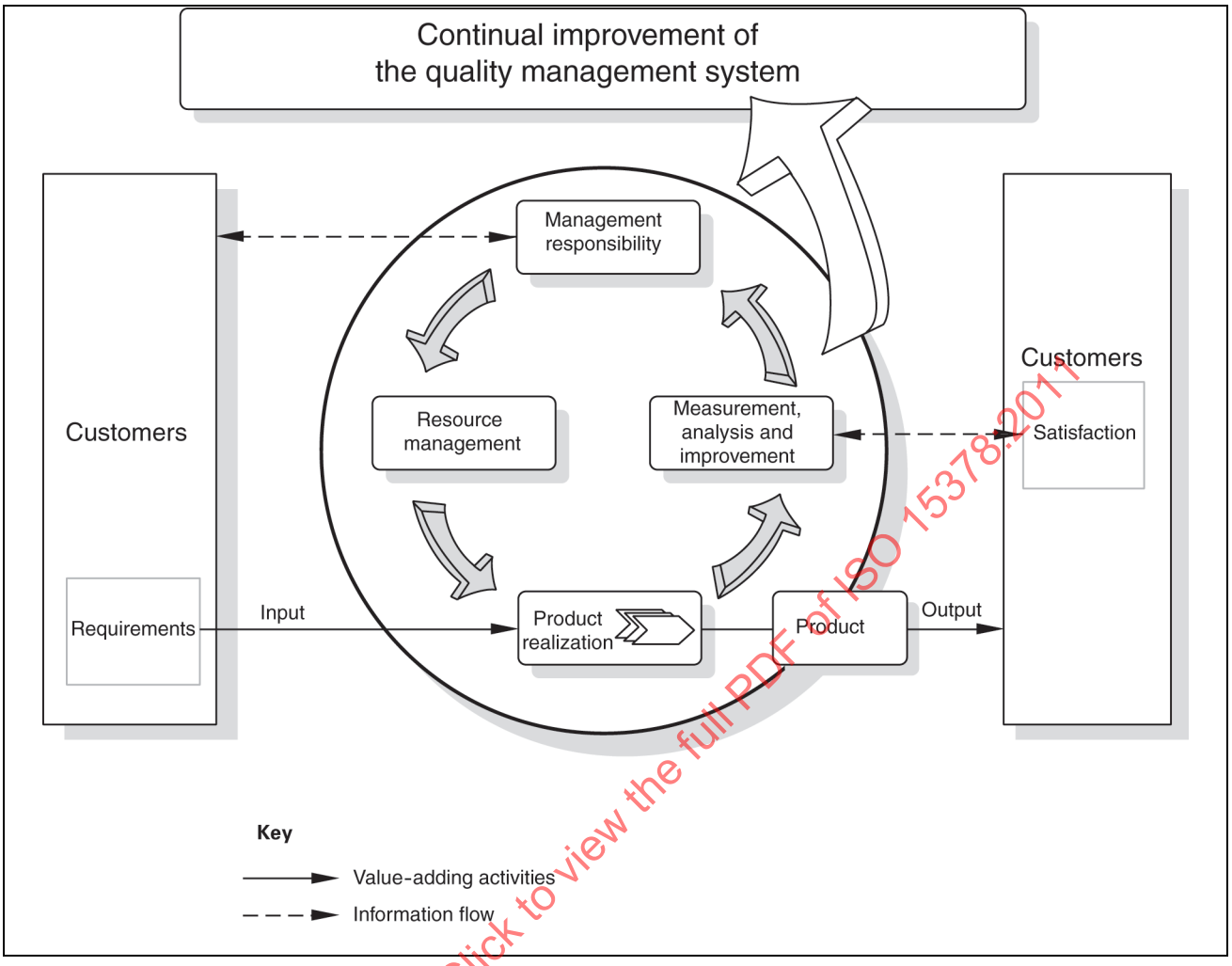

Figure 1 — Model of a process-based quality management system

0.3 Relationship with ISO 9004

ISO 9001:2008, Quality management systems — Requirements

0.3 Relationship with ISO 9004

ISO 9001 and ISO 9004 are quality management system standards which have been designed to complement each other, but can also be used independently.

ISO 9001 specifies requirements for a quality management system that can be used for internal application by organizations, or for certification, or for contractual purposes. It focuses on the effectiveness of the quality management system in meeting customer requirements.

At the time of publication of this International Standard, ISO 9004 is under revision. The revised edition of ISO 9004 will provide guidance to management for achieving sustained success for any organization in a complex, demanding, and ever changing, environment. ISO 9004 provides a wider focus on quality management than ISO 9001; it addresses the needs and expectations of all interested parties and their satisfaction, by the systematic and continual improvement of the organization's performance. However, it is not intended for certification, regulatory or contractual use.

0.4 Compatibility with other management systems

This International Standard incorporates the requirements of ISO 9001:2008 and, additionally, particular requirements for primary packaging materials, which are derived and adapted, as appropriate, from Good Manufacturing Practices for the production and control of medicinal products.

ISO 9001:2008, Quality management systems — Requirements

0.4 Compatibility with other management systems

During the development of this International Standard, due consideration was given to the provisions of ISO 14001:2004 to enhance the compatibility of the two standards for the benefit of the user community. Annex A shows the correspondence between ISO 9001:2008 and ISO 14001:2004.

This International Standard does not include requirements specific to other management systems, such as those particular to environmental management, occupational health and safety management, financial management or risk management. However, this International Standard enables an organization to align or integrate its own quality management system with related management system requirements. It is possible for an organization to adapt its existing management system(s) in order to establish a quality management system that complies with the requirements of this International Standard.

Primary packaging materials for medicinal products — Particular requirements for the application of ISO 9001:2008, with reference to Good Manufacturing Practice (GMP)

1 Scope

1.1 General

This International Standard specifies requirements for a quality management system where an organization needs to demonstrate its ability to provide primary packaging materials for medicinal products, which consistently meet customer requirements, including regulatory requirements and International Standards applicable to primary packaging materials.

In this International Standard the term "if appropriate" is used several times. When a requirement is qualified by this phrase, it is deemed to be "appropriate" unless the organization can document a justification otherwise.

ISO 9001:2008, Quality management systems — Requirements

1.1 General

This International Standard specifies requirements for a quality management system where an organization

a) needs to demonstrate its ability to consistently provide product that meets customer and applicable statutory and regulatory requirements, and

b) aims to enhance customer satisfaction through the effective application of the system, including processes for continual improvement of the system and the assurance of conformity to customer and applicable statutory and regulatory requirements.

NOTE 1 In this International Standard, the term "product" only applies to

a) product intended for, or required by, a customer,

b) any intended output resulting from the product realization processes.

NOTE 2 Statutory and regulatory requirements can be expressed as legal requirements.

1.2 Application

This International Standard is an application standard for the design, manufacture and supply of primary packaging materials for medicinal products. It is also applicable for certification purposes.

ISO 9001:2008, Quality management systems — Requirements

1.2 Application

All requirements of this International Standard are generic and are intended to be applicable to all organizations, regardless of type, size and product provided.

Where any requirement(s) of this International Standard cannot be applied due to the nature of an organization and its product, this can be considered for exclusion.

Where exclusions are made, claims of conformity to this International Standard are not acceptable unless these exclusions are limited to requirements within Clause 7, and such exclusions do not affect the organization's ability, or responsibility, to provide product that meets customer and applicable statutory and regulatory requirements.

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 9001:2008, Quality management systems — Requirements

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 9000:2005, *Quality management systems — Fundamentals and vocabulary*

ISO 14644-1:— [1], *Cleanrooms and associated controlled environments — Part 1: Classification of air cleanliness by particle concentration*

ISO 14644-2, Cleanrooms and associated controlled environments — Part 2: Specifications for monitoring and periodic testing to prove continued compliance with ISO 14644-1

ISO 14644-3, *Cleanrooms and associated controlled environments — Part 3: Test methods*

ISO 14644-5, Cleanrooms and associated controlled environments — Part 5: Operations

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 9000 apply.

1) To be published. (Revision of ISO 14644-1:1999)

ISO 9001:2008, Quality management systems — Requirements

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 9000 apply.

Throughout the text of this International Standard, wherever the term “product” occurs, it can also mean “service”.

Additional terms and definitions used in this International Standard are specific to Good Manufacturing Practices applicable to the manufacture of primary packaging materials for medicinal products.

3.1
air-lock
enclosed space to control air-flow

NOTE The space typically has at least two interlocked doors between two or more rooms, used either by people or for goods, to control for different conditions, e.g. cleanliness, air-flow upon entering.

3.2
approved
confirmed conformity status

NOTE Conformity can be confirmed for any stage of the process (starting materials, process aids, packaging material or finished product).

3.3
assembly
*fitting together of **primary packaging materials** (3.35.1) and/or components*

NOTE Examples may include pipette assemblies for filling, prepared components of injection systems or positioning of needle shields on prefillable syringes.

3.4
automated inspection
conformity evaluation performed by inspection equipment without manual intervention

NOTE The inspection equipment can include optoelectronics (cameras), laser systems, ultrasonics and their associated data processing functions or others.

3.5
batch
lot
*defined quantity of **primary packaging material** (3.35.1) manufactured in one process or series of processes intended to have uniform characteristics with consistent, homogeneous quality*

NOTE 1 To meet production requirements or customer needs, a batch can be divided up into a number of sub-batches that are later combined to form a single, consistent batch.

NOTE 2 In the case of continuous production, the batch is a fraction of the production defined either as a fixed quantity or as the amount produced in a fixed time interval.

3.6
batch document
batch record
*documents and records that provide a history of the **batch** (3.5), including information relating to its production and control, and which facilitate its **traceability** (3.63)*

3.7
batch number
lot number
*unique identifier to identify a **batch** or **lot** (3.5)*

NOTE A batch number can be a combination of numbers, letters and/or symbols which identifies a batch (or lot) and from which the production and distribution history can be determined.

3.8
batch release
*decision to release the **batch** (3.5) for sale or supply, following a formal review of the **batch document** (3.6) performed by the **quality unit** (3.41) or a person authorized by the quality unit(s)*

3.9
calibration
process of checking or adjusting (by comparison with a reference standard) the accuracy of a measuring instrument

NOTE Calibration can also be described as the set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or values represented by a material measure, and the corresponding known values of a reference standard.

3.10
change control
documented control of changes

NOTE Changes can include, for example, changes in raw materials, specifications, facilities, equipment, production processes and test methods.

3.11
cleanroom
room in which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room, and in which other relevant parameters, e.g. temperature, humidity, and pressure, are controlled as necessary

[ISO 14644-1:—, 3.1.1]

3.12
clean zone
dedicated space in which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the zone, and in which other relevant parameters, e.g. temperature, humidity, and pressure, are controlled as necessary

[ISO 14644-1:—, 3.1.2]

NOTE This zone may be open or enclosed and may or may not be located within a cleanroom.

3.13
contamination
*introduction of any unwanted material into the **primary packaging material** (3.35.1)*

NOTE 1 A finished product can be contaminated by physical (particulate), chemical or biological (bio- and endotoxin burden) action.

NOTE 2 Contamination can occur during production, packaging, storage and/or distribution from contaminated air systems, personnel, sampling equipment, materials, premises or containers.

3.14
controlled area
controlled environment
area or environment constructed and operated to control the possible introduction of potential contaminants

NOTE 1 The area is typically constructed and operated to control the introduction of potential contamination and the consequences of accidental release of living organisms.

NOTE 2 An appropriate pressure differential allows for the efficient removal of airborne contaminants, potential contamination and the consequences of accidental release.

3.15
cross-contamination
mix-up
contamination *(3.13) of a material or of a product with another material or product*

NOTE 1 Cross-contamination may also be referred to as admixture.

NOTE 2 See Reference [24].

3.16
customer complaint
information provided by a customer about deficiencies and/or nonconformities

NOTE 1 The information may be verbally communicated or written.

NOTE 2 The subject of a complaint can include primary packaging material quality, quantity or supply.

3.17
date of manufacture
date on which one of the first stages in the process of manufacture of the primary packaging material, or the packaging, or the final release, occurs, and which may be subject to customer agreement

3.18
deviation
departure from an approved ***standard operating procedure (SOP)*** *(3.58) or established standard*

3.19
documented procedure
procedure that is established, documented, authorized, implemented and maintained

3.20
double-check
documented ***verification*** *(3.65) of an activity, result or record by a second person or system*

NOTE A second in-process control check signature, production and quality records for a batch signed by a second person or electronic checks can be part of this verification process. Typically, double-checks are signed by a second person.

3.21
expiration date
expected suitable use limit

NOTE 1 See also definition ***shelf-life*** *(3.56).*

NOTE 2 This is typically the period during which a primary packaging material is expected to remain suitable for use if stored under defined conditions and after which it should not be used.

3.22
final inspection
*tests carried out on the **finished product** (3.23) to determine compliance with the specification*

3.23
finished product
***primary packaging material** (3.35.1) which has completed all stages of **production** (3.37)*

3.24
Good Manufacturing Practice
GMP
*quality control and quality assurance applied in **manufacturing** (3.29)*

NOTE 1 For the definitions of quality control and quality assurance, see ISO 9000:2005 (3.2.10 and 3.2.11).

NOTE 2 Requirements for Good Manufacturing Practice in the pharmaceutical industry are specified in a quality assurance standard, see Reference [24].

NOTE 3 Good Manufacturing Practice (GMP) for primary packaging materials requires, in addition to suitable provision of personnel, premises and equipment, a quality management system that includes controls for incoming starting materials, manufacture, corresponding documentation, factory hygiene, final inspection, records of distribution, processing of complaints and self-inspection.

NOTE 4 GMP and current Good Manufacturing Practice (cGMP) are equivalent. GMP guidelines are continually updated to the ever-changing requirements of the state-of-the-art. This has resulted in the term cGMP sometimes being used. The pharmaceutical industry expects that organizations take account of current GMP within their continual improvement programmes.

3.25
homogeneity
uniformity of characteristics and their values throughout a defined quantity of material

NOTE Homogeneity can include uniformity of materials or certain characteristics of materials of special significance.

3.26
in-process control
actions taken during the production process to test product conformity to its specification

NOTE 1 Monitoring processes and adjusting the means of production can be necessary to meet product requirements.

NOTE 2 The control of the environment or equipment can also be regarded as a part of in-process control.

3.27
intermediate product
***primary packaging material** (3.35.1) which has completed some but not all production stages*

NOTE An intermediate product needs further processing before it becomes a finished product.

3.28
line clearance
removal (line purge) of everything associated with the prior production run

NOTE Typically, line clearance is done prior to a production run to prevent any error and cross-contamination. Typically, it is required that a production facility (line) and its associated working area are completely clear of all materials, waste, products, samples, documents, etc. used in the previous production run before the introduction of materials, product samples, documents, etc. needed for the commencement of the next production run.

3.29
manufacturing
*all operations of purchase of materials and **primary packaging materials** (3.35.1), **production** (3.37), **quality control** (3.39), release, storage, distribution of products and the related controls*

3.30
medicinal product
any substance or combination of substances presented for treating or preventing disease in human beings or animals

NOTE 1 Any substance or combination of substances that may be administrated to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals is likewise considered a medicinal product.

NOTE 2 See Reference [24].

NOTE 3 Medicinal products may also be referred to as pharmaceutical or drug products, including clinical trial products.

3.31
organization
group of people and facilities with an arrangement of responsibilities, authorities and relationships

[ISO 9000:2005, definition 3.3.1]

NOTE In this International Standard the organization is the company manufacturing the primary packaging material.

3.32
origination
artwork
all preparative activities prior to print

NOTE These include concept, design, graphics, reprographics, film, plate making, silk screens and digital files and masters.

3.33
out of specification
OOS
*test results that do not comply with the **specification** (3.57)*

3.34
outsourcing
*provision of all or part of a process by another **organization** (3.31)*

*NOTE Outsourcing is often referred to as subcontracting (see definition 3.61 "**subcontractor**").*

3.35 *Packaging materials*

3.35.1
primary packaging materials
packaging materials used in pharmaceutical packaging which will contain, seal or be used for dose application of a medicial product and which will have direct contact with the medicinal product

NOTE 1 Examples of primary packaging materials are glass, rubber, plastics, aluminium containers/components, films, foils, laminate containers/components. They may be combinations of different materials/components (e.g. syringes, aerosol valves).

NOTE 2 Primary packaging materials with limited contact, e.g. pipettes and syringes, are included within the scope of this International Standard.

NOTE 3 Primary packaging materials may be directly printed or decorated.

3.35.2
secondary packaging materials
non-contact packaging materials, which include printed or unprinted cartons, labels, leaflets or inserts (or outserts), over-wraps, and transit containers such as folding boxes

3.36
process aids
material used to facilitate process realization

NOTE The material is not included in the product specification and can be removed at or before the final processing stage.

EXAMPLES Mould release agents, compressed air, rolling lubricants.

3.37
production
*processes resulting in **primary packaging material** (3.35.1)*

NOTE The processes form the full production cycle, from receipt of starting materials through processing and packaging, to completion as a finished product.

3.38
qualification process
process to demonstrate the ability to fulfil specified requirements

[ISO 9000:2005, 3.8.6]

*NOTE Qualification and **validation** (see 3.64) comprise design qualification (DQ), installation qualification (IQ), operational qualification (OQ), site acceptance tests (SAT) and performance qualification as well as re-qualification and re-validation as appropriate. This activity can also be performed concurrently, by bracketing (matrix validation) and/or retrospectively.*

3.39
quality control
part of quality management focused on fulfilling quality requirements

[ISO 9000:2005, 3.2.10]

NOTE Quality control includes checking or testing that specifications are met.

3.40
quality critical
*parameter affecting **primary packaging material** (3.35.1) quality*

NOTE A material, process step or process condition, test requirement or any other relevant parameter can be considered to be quality critical if nonconformity to its requirements could have significant detrimental consequences.

3.41
quality unit
organizational unit which fulfils both quality assurance (QA) and quality control (QC) responsibilities

NOTE The quality unit(s) may consist of separate QA and QC units or of a single individual (or group), depending upon the size and structure of the organization.

3.42
quarantine
status of materials or products isolated pending a decision on their subsequent approval or rejection

NOTE Quarantined material is typically isolated by physical or other effective means.

3.43
realization
generic term which covers all processes required to achieve the desired output from design to product delivery

3.44
reconciliation
*comparison between the amount of **finished product** (3.23) theoretically and actually produced or used, making allowance for normal variation*

NOTE The comparison considers waste, samples or other losses inherent in the process.

3.45
reconditioning
processing or reprocessing primary packaging material to meet specification requirements

3.46
rejected
*status of **starting materials** (3.59), **process aids** (3.36), **intermediate products** (3.27) or **finished products** (3.23) whose test results do not comply with one or more of the requirements of the **specification** (3.57), and which have been deemed, usually by the **quality unit(s)** (3.41), as not suitable for use*

3.47
rejection
*process whereby **starting materials** (3.59), **process aids** (3.36), **intermediate products** (3.27) or **finished products** (3.23) which have been deemed, usually by the **quality unit(s)** (3.41), as not suitable for use*

3.48
reprocessing
repeating part of a production process

NOTE Continuation of part of a process after an in-process control test has shown that the part is incomplete, is considered to be part of the normal process, and is not considered reprocessing.

3.49
retained samples
*materials or **finished products** (3.23) stored for future reference*

NOTE These samples are generally taken in a sufficient amount and stored under recommended conditions for reference during a defined period of time.

3.50
return
*process for sending back **primary packaging material(s)** (3.35.1) to the **organization** (3.31)*

3.51
rework
action on a nonconforming product to make it conform to the requirements

[ISO 9000:2005, 3.6.7]

NOTE Sorting can be considered to be rework.

3.52
risk analysis
systematic use of available information to identify hazards and to estimate the risk

[ISO/IEC Guide 51:1999, 3.10]

3.53
risk assessment
*overall process comprising a **risk analysis** (3.52) and a **risk evaluation** (3.54)*

[ISO/IEC Guide 51:1999, 3.12]

3.54
risk evaluation
*procedure based on the **risk analysis** (3.52) to determine whether the tolerable risk has been achieved*

[ISO/IEC Guide 51:1999, 3.11]

3.55
risk management
systematic application of management policies, procedures and practices to the task of analysing, evaluating, controlling and monitoring risk

[ISO 14971:2007, 2.22]

3.56
shelf-life
*the period during which a **primary packaging material** (3.35.1) is expected to comply with the requirements (specifications) if stored under defined conditions and after which it should not be used*

*NOTE See also **expiration date** (3.21)*

3.57
specification
document stating requirements

[ISO 9000:2005, 3.7.3]

3.58
standard operating procedure
SOP
*authorized, documented procedure, or set of procedures, work instructions and test instructions for **production** (3.37) and control*

3.59
starting material
*raw material/components/substances used to produce **primary packaging materials** (3.35.1)*

3.60
sterile
state of being free from viable microorganisms

[ISO 14937:2009, 3.26]

3.61
subcontractor
*third party for outsourced work and services which contribute in full, or part, to the manufacture of **primary packaging materials** (3.35.1)*

3.62
surface treatment
process to improve primary packaging material surface

EXAMPLE Siliconization or other treatment of internal glass surfaces, coating of internal or external surfaces of glass containers or rubber parts.

3.63
traceability
ability to trace the history, application or location of that which is under consideration

NOTE 1 When considering a product, traceability can relate to

— *the origin of materials and parts,*

— *the processing history, and*

— *the distribution and location of the product after delivery.*

NOTE 2 In the field of metrology, the definition in VIM:1993, 6.10, is the accepted definition.

[ISO 9000:2005, 3.5.4)

3.64
validation
confirmation, through the provision of objective evidence that the requirements for a specific intended use or application have been fulfilled

[ISO 9000:2005, 3.8.5]

NOTE See note to 3.38.

3.65
verification
confirmation, through the provision of objective evidence that specified requirements have been fulfilled

[ISO 9000:2005, 3.8.4]

NOTE 1 The term "verified" is used to designate the corresponding status.

NOTE 2 In development and design, verification is the process of examining the results of an activity under consideration in order to establish whether said activity conforms to the specified requirements.

4 Quality management system

4.1 General requirements

ISO 9001:2008, Quality management systems — Requirements

4 Quality management system

4.1 General requirements

The organization shall establish, document, implement and maintain a quality management system and continually improve its effectiveness in accordance with the requirements of this International Standard.

The organization shall

a) determine the processes needed for the quality management system and their application throughout the organization (see 1.2),

b) determine the sequence and interaction of these processes,

c) determine criteria and methods needed to ensure that both the operation and control of these processes are effective,

d) ensure the availability of resources and information necessary to support the operation and monitoring of these processes,

e) monitor, measure where applicable, and analyse these processes, and

f) implement actions necessary to achieve planned results and continual improvement of these processes.

g) describe its overall policy, intentions and approach to assurance of product quality.

ISO 9001:2008, Quality management systems — Requirements

These processes shall be managed by the organization in accordance with the requirements of this International Standard.

Where an organization chooses to outsource any process that affects product conformity to requirements, the organization shall ensure control over such processes. The type and extent of control to be applied to these outsourced processes shall be defined within the quality management system.

NOTE 1 Processes needed for the quality management system referred to above include processes for management activities, provision of resources, product realization, measurement, analysis and improvement.

NOTE 2 An “outsourced process” is a process that the organization needs for its quality management system and which the organization chooses to have performed by an external party.

NOTE 3 Ensuring control over outsourced processes does not absolve the organization of the responsibility of conformity to all customer, statutory and regulatory requirements. The type and extent of control to be applied to the outsourced process can be influenced by factors such as

a) the potential impact of the outsourced process on the organization's capability to provide product that conforms to requirements,

b) the degree to which the control for the process is shared,

c) the capability of achieving the necessary control through the application of 7.4.

4.2 Documentation requirements

4.2.1 General

ISO 9001:2008, Quality management systems — Requirements

4.2.1 General

The quality management system documentation shall include

a) documented statements of a quality policy and quality objectives,

b) a quality manual,

c) documented procedures and records required by this International Standard, and

d) documents, including records, determined by the organization to be necessary to ensure the effective planning, operation and control of its processes.

NOTE 1 Where the term “documented procedure” appears within this International Standard, this means that the procedure is established, documented, implemented and maintained. A single document may address the requirements for one or more procedures. A requirement for a documented procedure may be covered by more than one document.

NOTE 2 The extent of the quality management system documentation can differ from one organization to another due to

a) the size of the organization and type of activities,

b) the complexity of processes and their interactions, and

c) the competence of personnel.

NOTE 3 The documentation can be in any form or type of medium.

NOTE 4 Documented procedures, work instructions and test instructions for production and control purposes required by this International Standard can be called standard operating procedures (SOPs).

The organization's overall policy, intentions and approach to validation shall be documented.

4.2.2 Quality manual

ISO 9001:2008, Quality management systems — Requirements

4.2.2 Quality manual

The organization shall establish and maintain a quality manual that includes

a) the scope of the quality management system, including details of and justification for any exclusions (see 1.2),

b) the documented procedures established for the quality management system, or reference to them, and

c) a description of the interaction between the processes of the quality management system.

4.2.2.1 *The organization shall clearly define the extent to which this International Standard is applicable to its processes.*

NOTE The organization can define whether this International Standard applies to all of its output products (for pharmaceutical and other uses) or to those for pharmaceutical use only.

4.2.2.2 *The quality manual shall outline the structure of the documentation used in the quality management system.*

4.2.3 Control of documents

ISO 9001:2008, Quality management systems — Requirements

4.2.3 Control of documents

Documents required by the quality management system shall be controlled. Records are a special type of document and shall be controlled according to the requirements given in 4.2.4.

A documented procedure shall be established to define the controls needed

a) to approve documents for adequacy prior to issue,

b) to review and update as necessary and re-approve documents,

c) to ensure that changes and the current revision status of documents are identified,

d) to ensure that relevant versions of applicable documents are available at points of use,

e) to ensure that documents remain legible and readily identifiable,

f) to ensure that documents of external origin determined by the organization to be necessary for the planning and operation of the quality management system are identified and their distribution controlled, and

g) to prevent the unintended use of obsolete documents, and to apply suitable identification to them if they are retained for any purpose.

4.2.3.1 *The organization shall ensure that changes to documents are reviewed and approved either by the original approving function or another designated function which has access to pertinent background information upon which to base its decisions.*

4.2.3.2 *The organization shall define the period for which at least one copy of obsolete, controlled documents shall be retained (see also 4.2.4.8).*

4.2.3.3 *If electronic signatures are used on documents, they shall be controlled to provide equivalent security to that given by a hand-written signature.*

4.2.3.4 *Controlled documents should include a unique identification (e.g. document title/number, issue and page number).*

4.2.4 Control of records

ISO 9001:2008, Quality management systems — Requirements

4.2.4 Control of records

Records established to provide evidence of conformity to requirements and of the effective operation of the quality management system shall be controlled.

The organization shall establish a documented procedure to define the controls needed for the identification, storage, protection, retrieval, retention and disposition of records.

Records shall remain legible, readily identifiable and retrievable.

NOTE Records comprise batch-related manufacturing data as well as other quality records such as deviation and investigation reports.

4.2.4.1 *Electronic records shall be subject to the same controls as those required for other records (see 4.2.4 and 7.5.2.9).*

4.2.4.2 *Entries in records shall be clear, indelible, made directly after performing the activity (in the order performed), dated, and initialled or signed by the person making the entry. Corrections for entries shall be dated, initialled or signed and, where appropriate, explained, leaving the original entry still legible.*

4.2.4.3 *The organization shall define the quality critical processes and parameters where a double-check is necessary for the release of a batch. If either check is carried out electronically this shall be clearly defined.*

4.2.4.4 *Each quality critical stage and parameter in production and control processes shall be identified and shall be double-checked.*

4.2.4.5 *For each batch of primary packaging material the organization shall establish and maintain a record that provides traceability (see 7.5.3) and identifies the quantity manufactured and quantity approved for distribution.*

4.2.4.6 *The organization shall define those parameters of the batch documentation that need to be verified.*

4.2.4.7 *The batch documentation shall be verified and approved.*

4.2.4.8 *All manufacturing, control, testing, distribution and investigation records shall be retained for at least five years after the date of manufacture or as agreed with the customer, or at least one year after the expiration date of the primary packaging material assigned by the organization, unless agreed otherwise with the customer.*

NOTE The records of the primary packaging material might need to be retained until the end of the shelf-life of the medicinal product as specified by the customer.

5 Management responsibility

5.1 Management commitment

ISO 9001:2008, Quality management systems — Requirements

5.1 Management commitment

Top management shall provide evidence of its commitment to the development and implementation of the quality management system and continually improve its effectiveness by

a) communicating to the organization the importance of meeting customer as well as statutory and regulatory requirements,

b) establishing the quality policy,

c) ensuring that quality objectives are established,

d) conducting management reviews, and

e) ensuring the availability of resources.

5.2 Customer focus

ISO 9001:2008, Quality management systems — Requirements

5.2 Customer focus

Top management shall ensure that customer requirements are determined and are met with the aim of enhancing customer satisfaction (see 7.2.1 and 8.2.1).

5.2.1 *Customer audits*

The organization shall permit the customer or their representatives (when mutually agreed) to conduct audits to review the quality management system.

Key customer requirements for organizations are suitable facilities, competent and trained personnel, processes designed to ensure product security and avoidance of cross-contamination and the ability to consistently produce product conforming to the customer specifications.

5.3 Quality policy

ISO 9001:2008, Quality management systems — Requirements

5.3 Quality policy

Top management shall ensure that the quality policy

a) is appropriate to the purpose of the organization,

b) includes a commitment to comply with requirements and continually improve the effectiveness of the quality management system,

c) provides a framework for establishing and reviewing quality objectives,

d) is communicated and understood within the organization, and

e) is reviewed for continuing suitability.

5.4 Planning

5.4.1 Quality objectives

ISO 9001:2008, Quality management systems — Requirements

5.4.1 Quality objectives

Top management shall ensure that quality objectives, including those needed to meet requirements for product [see 7.1 a)], are established at relevant functions and levels within the organization. The quality objectives shall be measurable and consistent with the quality policy.

5.4.2 Quality management system planning

ISO 9001:2008, Quality management systems — Requirements

5.4.2 Quality management system planning

Top management shall ensure that

a) the planning of the quality management system is carried out in order to meet the requirements given in 4.1, as well as the quality objectives, and

b) the integrity of the quality management system is maintained when changes to the quality management system are planned and implemented.

5.5 Responsibility, authority and communication

5.5.1 Responsibility and authority

ISO 9001:2008, Quality management systems — Requirements

5.5.1 Responsibility and authority

Top management shall ensure that responsibilities and authorities are defined and communicated within the organization.

5.5.1.1 *The organization shall maintain a current record (see 4.2.4) of signatures of responsible persons. Signature and/or user identification lists of all personnel checking or double-checking process steps, in-process controls, etc. are recommended.*

5.5.1.2 *The quality unit(s) with responsibility for quality critical decisions shall have the authority to make those decisions independently of production.*

5.5.2 Management representative

ISO 9001:2008, Quality management systems — Requirements

5.5.2 Management representative

Top management shall appoint a member of the organization's management who, irrespective of other responsibilities, shall have responsibility and authority that includes

a) ensuring that processes needed for the quality management system are established, implemented and maintained,

b) reporting to top management on the performance of the quality management system and any need for improvement, and

c) ensuring the promotion of awareness of customer requirements throughout the organization.

NOTE The responsibility of a management representative can include liaising with external parties on matters relating to the quality management system.

5.5.3 Internal communication

ISO 9001:2008, Quality management systems — Requirements

5.5.3 Internal communication

Top management shall ensure that appropriate communication processes are established within the organization and that communication takes place regarding the effectiveness of the quality management system.

5.5.3.1 *GMP in this International Standard and regulatory requirements shall be communicated, as appropriate, to each level of the organization.*

5.5.3.2 *Top management shall be notified of quality critical situations, in a timely manner.*

NOTE Examples of communication processes include those related to the communication of the quality policy, management review, internal quality audit results, and corrective and preventive actions.

5.6 Management review

5.6.1 General

ISO 9001:2008, Quality management systems — Requirements

5.6.1 General

Top management shall review the organization's quality management system, at planned intervals, to ensure its continuing suitability, adequacy and effectiveness. This review shall include assessing opportunities for improvement and the need for changes to the quality management system, including the quality policy and quality objectives.

Records from management reviews shall be maintained (see 4.2.4).

5.6.2 Review input

ISO 9001:2008, Quality management systems — Requirements

5.6.2 Review input

The input to management review shall include information on

a) results of audits,

b) customer feedback,

c) process performance and product conformity,

d) status of preventive and corrective actions,

e) follow-up actions from previous management reviews,

f) changes that could affect the quality management system, and

g) recommendations for improvement.

h) effectiveness of training.

5.6.3 Review output

ISO 9001:2008, Quality management systems — Requirements

5.6.3 Review output

The output from the management review shall include any decisions and actions related to

a) improvement of the effectiveness of the quality management system and its processes,

b) improvement of product related to customer requirements, and

c) resource needs.

6 Resource management

6.1 Provision of resources

ISO 9001:2008, Quality management systems — Requirements

6.1 Provision of resources

The organization shall determine and provide the resources needed

a) to implement and maintain the quality management system and continually improve its effectiveness, and

b) to enhance customer satisfaction by meeting customer requirements.

6.2 Human resources

6.2.1 General

ISO 9001:2008, Quality management systems — Requirements

6.2.1 General

Personnel performing work affecting conformity to product requirements shall be competent on the basis of appropriate education, training, skills and experience.

NOTE Conformity to product requirements can be affected directly or indirectly by personnel performing any task within the quality management system.

6.2.2 Competence, training and awareness

ISO 9001:2008, Quality management systems — Requirements

6.2.2 Competence, training and awareness

The organization shall

a) determine the necessary competence for personnel performing work affecting conformity to product requirements,

b) where applicable, provide training or take other actions to achieve the necessary competence,

c) evaluate the effectiveness of the actions taken,

d) ensure that its personnel are aware of the relevance and importance of their activities and how they contribute to the achievement of the quality objectives, and

e) maintain appropriate records of education, training, skills and experience (see 4.2.4).

6.2.2.1 GMP training

6.2.2.1.1 *Additional training shall be conducted regularly and include awareness of applicable GMP and all procedures and policies that affect product quality and the quality management system. This training shall include*

a) *the risk of contamination and cross-contamination,*

b) *the potential hazard to end user/patient if product is contaminated, and*

c) *the impact of any deviations from specified procedures, processes or specifications on customer's product quality or on the end user.*

6.2.2.1.2 *Particular attention shall be given to the training of the personnel involved with the manufacture of sterile components or components to be subsequently sterilized.*

6.2.2.1.3 *Specific training on microbiological and particulate contamination and the potential risk to the patient of such contamination shall be provided.*

6.2.2.1.4 *Additional refresher training shall be carried out at defined intervals.*

6.2.2.1.5 *Temporary personnel shall be trained or be under the supervision of a trained person.*

6.2.2.1.6 *Where consultants are employed to advise on quality matters, records of their qualifications and type of service(s) provided shall be maintained.*

6.3 Infrastructure

ISO 9001:2008, Quality management systems — Requirements

6.3 Infrastructure

The organization shall determine, provide and maintain the infrastructure needed to achieve conformity to product requirements. Infrastructure includes, as applicable,

a) buildings, workspace and associated utilities,

b) process equipment (both hardware and software), and

c) supporting services (such as transport, communication or information systems).

6.4 Work environment

ISO 9001:2008, Quality management systems — Requirements

6.4 Work environment

The organization shall determine and manage the work environment needed to achieve conformity to product requirements.

NOTE The term “work environment” relates to those conditions under which work is performed including physical, environmental and other factors (such as noise, temperature, humidity, lighting or weather).

6.4.1 *Working environment requirements*

6.4.1.1 *The organization shall establish documented requirements for health, cleanliness, clothing and access control of personnel, if contact between such personnel and the primary packaging material or work environment could adversely affect the quality of the primary packaging material.*

6.4.1.2 *If work environment conditions can have an adverse effect on primary packaging material quality, the organization shall define the appropriate work environment conditions and establish a system for their effective monitoring and control.*

6.4.1.3 *If appropriate, special conditions shall be established and documented for the control of contaminated or potentially contaminated primary packaging material to prevent contamination of other primary packaging material, the work environment or personnel.*

6.4.2 *Classification of clean zones/cleanrooms*

Clean zones/cleanrooms shall be classified according to ISO 14644-1, and monitored/operated according to ISO 14644-2, ISO 14644-3 and ISO 14644-5 or equivalent.

For cleanroom design, construction and start-up, see ISO 14644-2 and ISO 14644-4.

Monitoring may be conducted in accordance with ISO 14698-1 and ISO 14698-2.

6.4.3 *Risk control of contamination*

The organization shall determine and control the risks that may result in contamination of primary packaging materials, for example:

a) *personal hygiene and health;*

b) *personal clothing, jewellery including piercings, and make-up;*

c) *smoking, eating, chewing, drinking, and personal medication;*

d) *handling and disposal of waste;*

e) *microbiological contamination.*

6.4.4 *Pest control*

An effective, documented pest control programme shall be implemented and maintained.

6.4.5 *Utilities (ancillary services)*

6.4.5.1 *All utilities (e.g. air, gases, steam, water) shall be assessed for their potential impact on the quality of the primary packaging materials and any associated risks. Records of the assessment shall be maintained (see 4.2.4).*

The assessment should include other fluids (e.g. lubrication fluids, cooling fluids, hydraulic oils, etc.), which may accidentally come into contact with the primary packaging material.

Dependent on the risks, the use of food-grade fluids should be considered.

6.4.5.2 *Appropriate ventilation and exhaust systems shall be provided, where necessary, to minimize contamination. Particular attention shall be given to recirculation systems.*

6.4.5.3 *If water comes into direct contact with the primary packaging material, or its starting material, or is used for cleaning the equipment in contact with the product, its quality shall be determined and controlled.*

6.5 *Maintenance activities*

6.5.1 *The organization shall establish documented requirements for maintenance activities (e.g. production processes, systems and equipment), when such activities or lack thereof may affect product quality.*

6.5.2 *Records of such maintenance shall be maintained (see 4.2.4).*

6.5.3 *The organization shall ensure that the infrastructure is managed, operated, cleaned and, where appropriate, maintained in accordance with GMP and so as to avoid product contamination (including control of particulate matter and microbiological control where applicable).*

6.5.4 *Computerized systems that may impact upon primary packaging material quality shall have sufficient controls for installation, operation, maintenance, modification and security.*

6.5.5 *A set of technical documentation for quality critical equipment and installations shall be maintained.*

7 Product realization

7.1 Planning of product realization

ISO 9001:2008, Quality management systems — Requirements

7.1 Planning of product realization

The organization shall plan and develop the processes needed for product realization. Planning of product realization shall be consistent with the requirements of the other processes of the quality management system (see 4.1).

In planning product realization, the organization shall determine the following, as appropriate:

a) quality objectives and requirements for the product;

b) the need to establish processes and documents, and to provide resources specific to the product;

c) required verification, validation, monitoring, measurement, inspection and test activities specific to the product and the criteria for product acceptance;

d) records needed to provide evidence that the realization processes and resulting product meet requirements (see 4.2.4).

The output of this planning shall be in a form suitable for the organization's method of operations.

NOTE 1 A document specifying the processes of the quality management system (including the product realization processes) and the resources to be applied to a specific product, project or contract can be referred to as a quality plan.

NOTE 2 The organization may also apply the requirements given in 7.3 to the development of product realization processes.

7.1.1 *Product realization planning shall consider the requirement for consistent processing of primary packaging materials. Planning shall also take account of the need for taking and retaining samples in appropriate conditions.*

7.1.2 *The organization shall ensure that risk management processes are included in the planning and implemented throughout product realization; records shall be maintained (see 4.2.4).*

7.2 Customer-related processes

7.2.1 Determination of requirements related to the product

ISO 9001:2008, Quality management systems — Requirements

7.2.1 Determination of requirements related to the product

The organization shall determine

a) requirements specified by the customer, including the requirements for delivery and post-delivery activities,

b) requirements not stated by the customer but necessary for specified or intended use, where known,

c) statutory and regulatory requirements applicable to the product, and

d) any additional requirements considered necessary by the organization.

NOTE Post-delivery activities include, for example, actions under warranty provisions, contractual obligations such as maintenance services, and supplementary services such as recycling or final disposal.

7.2.1.1 *Requirements related to the product, including changes requiring notification, shall be determined and documented.*

7.2.1.2 *Customer requirements to avoid unauthorized use of waste primary packaging material (including samples, print media, labels) shall be determined and documented.*

7.2.2 Review of requirements related to the product

ISO 9001:2008, Quality management systems — Requirements

7.2.2 Review of requirements related to the product

The organization shall review the requirements related to the product. This review shall be conducted prior to the organization's commitment to supply a product to the customer (e.g. submission of tenders, acceptance of contracts or orders, acceptance of changes to contracts or orders) and shall ensure that

a) product requirements are defined,

b) contract or order requirements differing from those previously expressed are resolved, and

c) the organization has the ability to meet the defined requirements.

Records of the results of the review and actions arising from the review shall be maintained (see 4.2.4).

Where the customer provides no documented statement of requirement, the customer requirements shall be confirmed by the organization before acceptance.

Where product requirements are changed, the organization shall ensure that relevant documents are amended and that relevant personnel are made aware of the changed requirements.

NOTE In some situations, such as internet sales, a formal review is impractical for each order. Instead the review can cover relevant product information such as catalogues or advertising material.

7.2.3 Customer communication

ISO 9001:2008, Quality management systems — Requirements

7.2.3 Customer communication

The organization shall determine and implement effective arrangements for communicating with customers in relation to

a) product information,

b) enquiries, contracts or order handling, including amendments, and

c) customer feedback, including customer complaints.

7.2.3.1 *The organization shall establish and maintain a documented feedback system to provide early warning of potential and actual quality problems and to facilitate customer input into the corrective and preventive action system.*

7.2.3.2 *When required by the customer, the organization shall agree with the customer which changes require written confirmation prior to approval and which changes require notification only. Proposed changes shall be communicated in a timely manner and the process for introducing changes agreed (see 7.2.1).*

It is recommended that, between the organization and the customer, there is a documented technical/quality assurance agreement that includes the action to be taken for nonconformities (see 8.3).

7.3 Design and development

7.3.1 Design and development planning

ISO 9001:2008, Quality management systems — Requirements

7.3.1 Design and development planning

The organization shall plan and control the design and development of product.

During the design and development planning, the organization shall determine

a) the design and development stages,

b) the review, verification and validation that are appropriate to each design and development stage, and

c) the responsibilities and authorities for design and development.

The organization shall manage the interfaces between different groups involved in design and development to ensure effective communication and clear assignment of responsibility.

Planning output shall be updated, as appropriate, as the design and development progresses.

NOTE Design and development review, verification and validation have distinct purposes. They can be conducted and recorded separately or in any combination, as suitable for the product and the organization.

7.3.1.1 *The organization shall implement documented procedures for design and development. These procedures shall include risk assessment, determination of relevant aspects of GMP and any potential impact on the customer and ultimately the patient.*

7.3.1.2 *The responsibility for design and risk assessment should be agreed between the customer and the organization.*

7.3.1.3 *During the design and development process, it should be ensured that design and development outputs are verified as suitable before finalizing production specifications.*

7.3.2 Design and development inputs

ISO 9001:2008, Quality management systems — Requirements

7.3.2 Design and development inputs

Inputs relating to product requirements shall be determined and records maintained (see 4.2.4). These inputs shall include

a) functional and performance requirements,

b) applicable statutory and regulatory requirements,

c) where applicable, information derived from previous similar designs, and

d) other requirements essential for design and development.

The inputs shall be reviewed for adequacy. Requirements shall be complete, unambiguous and not in conflict with each other.

7.3.3 Design and development outputs

ISO 9001:2008, Quality management systems — Requirements

7.3.3 Design and development outputs

The outputs of design and development shall be in a form suitable for verification against the design and development input and shall be approved prior to release.

Design and development outputs shall

a) meet the input requirements for design and development,

b) provide appropriate information for purchasing, production and service provision,

c) contain or reference product acceptance criteria, and

d) specify the characteristics of the product that are essential for its safe and proper use.

NOTE Information for production and service provision can include details for the preservation of product.

7.3.4 Design and development review

ISO 9001:2008, Quality management systems — Requirements

7.3.4 Design and development review

At suitable stages, systematic reviews of design and development shall be performed in accordance with planned arrangements (see 7.3.1)

a) to evaluate the ability of the results of design and development to meet requirements, and

b) to identify any problems and propose necessary actions.

Participants in such reviews shall include representatives of functions concerned with the design and development stage(s) being reviewed. Records of the results of the reviews and any necessary actions shall be maintained (see 4.2.4).

7.3.5 Design and development verification

ISO 9001:2008, Quality management systems — Requirements

7.3.5 Design and development verification

Verification shall be performed in accordance with planned arrangements (see 7.3.1) to ensure that the design and development outputs have met the design and development input requirements. Records of the results of the verification and any necessary actions shall be maintained (see 4.2.4).

7.3.6 Design and development validation

ISO 9001:2008, Quality management systems — Requirements

7.3.6 Design and development validation

Design and development validation shall be performed in accordance with planned arrangements (see 7.3.1) to ensure that the resulting product is capable of meeting the requirements for the specified application or intended use, where known. Wherever practicable, validation shall be completed prior to the delivery or implementation of the product. Records of the results of validation and any necessary actions shall be maintained (see 4.2.4).

7.3.7 Control of design and development changes

ISO 9001:2008, Quality management systems — Requirements

7.3.7 Control of design and development changes

Design and development changes shall be identified and records maintained. The changes shall be reviewed, verified and validated, as appropriate, and approved before implementation. The review of design and development changes shall include evaluation of the effect of the changes on constituent parts and product already delivered. Records of the results of the review of changes and any necessary actions shall be maintained (see 4.2.4).

7.3.7.1 *Notification*

Changes that affect any of the data supplied shall be reported to the customer and, if a technical dossier/master file has been supplied by the organization, directly to the regulatory authorities.

7.3.7.2 *Design change*

When implementing change, the existing validation and documents affected by the change shall be reviewed and revised; personnel shall be retrained as appropriate.

NOTE 1 Design and development outputs can include records (specifications, manufacturing procedures, engineering drawings, engineering or research logbooks) and samples.

NOTE 2 Confidential scientific and technical information (of the organization) can be supplied as a dossier directly to the regulatory authorities (e.g. technical dossier and/or master file).

7.4 Purchasing

7.4.1 Purchasing process

ISO 9001:2008, Quality management systems — Requirements

7.4.1 Purchasing process

The organization shall ensure that purchased product conforms to specified purchase requirements. The type and extent of control applied to the supplier and the purchased product shall be dependent upon the effect of the purchased product on subsequent product realization or the final product.

The organization shall evaluate and select suppliers based on their ability to supply product in accordance with the organization's requirements. Criteria for selection, evaluation and re-evaluation shall be established. Records of the results of evaluations and any necessary actions arising from the evaluation shall be maintained (see 4.2.4).

7.4.1.1 *The organization shall approve suppliers of*

a) starting materials,

b) quality critical process aids, and

c) packaging materials for use in cleanrooms.

7.4.1.2 *The organization shall notify the customer prior to outsourcing any part of the production process.*

7.4.1.3 *All outsourced services that can affect product quality shall be controlled, including origination (artwork), laboratory services, sterilization, calibration services and qualification services, maintenance, cleaning, haulage, pest control and waste contractors, depending on the risks involved.*

7.4.1.4 *Consultants advising on the production and control of primary packaging materials shall be considered as suppliers.*

7.4.1.5 *Suppliers of quality critical materials and services shall be approved by the quality unit(s) or a person assigned by the quality unit(s).*

7.4.1.6 *The organization shall evaluate and record the competence of laboratories to perform quality critical activities. The organization shall only use laboratories that it has accepted as being competent, to perform quality critical activities.*

7.4.1.7 *If the sterilization process is outsourced, the organization shall ensure that the process complies with the requirements of 7.5.1 and 7.5.2.*

7.4.1.8 *Changing the source of quality critical raw materials shall be subject to change control.*

7.4.2 Purchasing information

ISO 9001:2008, Quality management systems — Requirements

7.4.2 Purchasing information

Purchasing information shall describe the product to be purchased, including, where appropriate,

a) requirements for approval of product, procedures, processes and equipment,

b) requirements for qualification of personnel, and

c) quality management system requirements.

The organization shall ensure the adequacy of specified purchase requirements prior to their communication to the supplier.

7.4.2.1 *The organization shall maintain relevant purchasing information, i.e. documents (see 4.2.3) and records (see 4.2.4), to the extent required for traceability as given in 7.5.3.*

7.4.3 Verification of purchased product

ISO 9001:2008, Quality management systems — Requirements

7.4.3 Verification of purchased product

The organization shall establish and implement the inspection or other activities necessary for ensuring that purchased product meets specified purchase requirements.

Where the organization or its customer intends to perform verification at the supplier's premises, the organization shall state the intended verification arrangements and method of product release in the purchasing information.

7.4.3.1 *Incoming materials shall be physically or administratively quarantined until they have been approved and released for use.*

NOTE In exceptional circumstances, material under test can be used, provided there are fail-safe procedures in place to prevent the release of primary packaging material, until the status of those materials has been confirmed.

7.4.3.2 *Records of the verification shall be maintained (see 4.2.4).*

7.4.3.3 *Sampling activities shall be conducted in accordance with a sampling method, using procedures, facilities and equipment designed to avoid contamination.*

7.5 Production and service provision

7.5.1 Control of production and service provision

ISO 9001:2008, Quality management systems — Requirements

7.5.1 Control of production and service provision

The organization shall plan and carry out production and service provision under controlled conditions. Controlled conditions shall include, as applicable,

a) the availability of information that describes the characteristics of the product,

b) the availability of work instructions, as necessary,

c) the use of suitable equipment,

d) the availability and use of monitoring and measuring equipment,

e) the implementation of monitoring and measurement, and

f) the implementation of product release, delivery and post-delivery activities.

g) the definition of the date of manufacture, taking into account the processes involved,

h) special attention to marking, labelling and packaging operations to provide effective control and to prevent errors,

i) a documented procedure defining the management of process deviations. The quality critical deviations shall be investigated and the outcome recorded (see 4.2.4).

7.5.1.1 *Cleanliness of product and contamination control*

7.5.1.1.1 *The organization shall establish and maintain documented requirements for cleanliness of primary packaging materials and procedures to prevent contamination of equipment or product.*

The potential risks associated with any materials or process aids which may carry a risk to patient safety, e.g. transmissible spongiform encephalopathies (TSE), should be evaluated.

7.5.1.1.2 *All production processes in clean zones or in controlled areas, including environmental controls, production, in-process controls and packaging of primary packaging materials shall comply with the specified area conditions and operating criteria. Cleanrooms shall have air-locks.*

7.5.1.1.3 *Production processes in controlled environmental conditions shall be agreed between customer and organization.*

7.5.1.1.4 *The organization shall also establish documented cleanliness requirements for primary packaging materials when*

a) primary packaging material is cleaned by the organization prior to sterilization by the organization and/or its use, or

b) primary packaging material is to be supplied non-sterile and its cleanliness is of significance in use, or

c) process agents are to be removed from product during manufacture.

7.5.1.1.5 *Storage containers and their attendant manifolds, and filling and discharge lines shall be identified.*

7.5.1.1.6 *Special attention (e.g. identification, security, cleanliness) shall be given prior to discharge in and out of bulk containers/silos.*

7.5.1.1.7 *Written procedures shall be established for the cleaning of equipment used in the production of primary packaging materials. Records of cleaning equipment that are critical to the quality of primary packaging materials shall be maintained (see 4.2.4).*

7.5.1.1.8 *Production equipment/areas shall be identified as to content and cleaning status.*

7.5.1.1.9 *The incorporation of reprocessed materials is inherent in the manufacture of some materials (e.g. glass, aluminium, paper, thermoplastics). Reprocessing parameters shall be defined and agreed with the customer.*

7.5.1.1.10 *Unless agreed with the customer, thermoplastic materials shall not be reground and reused in primary packaging materials.*

7.5.1.1.11 *There shall be a line clearance inspection between different batches to remove all materials and documentation not required for the next operation. Line clearance activities shall be recorded (see 4.2.4).*

7.5.1.2 *Change control*

7.5.1.2.1 *The organization shall implement a process for effective and efficient control of changes to ensure that changes do not adversely affect product quality, and that they do satisfy the needs and expectations of interested parties.*

7.5.1.2.2 *Changes shall be identified, recorded, evaluated, reviewed and controlled in order to understand the effect on other processes.*

7.5.1.2.3 *Authority for initiating, review and approval of changes shall be defined in order to maintain control.*

7.5.1.3 *Particular requirements for sterile primary packaging materials*

The organization shall maintain records (see 4.2.4) of the process parameters for the sterilization process, which was used for each sterilization batch. Sterilization records shall be traceable to each batch of primary packaging material.

7.5.2 Validation of processes for production and service provision

ISO 9001:2008, Quality management systems — Requirements

7.5.2 Validation of processes for production and service provision

The organization shall validate any processes for production and service provision where the resulting output cannot be verified by subsequent monitoring or measurement and, as a consequence, deficiencies become apparent only after the product is in use or the service has been delivered.

Validation shall demonstrate the ability of these processes to achieve planned results.

The organization shall establish arrangements for these processes including, as applicable,

a) defined criteria for review and approval of the processes,

b) approval of equipment and qualification of personnel,

c) use of specific methods and procedures,

d) requirements for records (see 4.2.4), and

e) revalidation.

7.5.2.1 *The organization shall identify the quality critical processes within its operations, namely those that influence the quality of the primary packaging material. Control over any of these processes where the resulting output cannot be verified by subsequent monitoring or measurement shall be demonstrated through validation and documented.*

7.5.2.2 *Risk assessment shall be used to determine which processes are quality critical, and to determine the extent of the validation work necessary to demonstrate control of these processes. Risk analysis shall be related to product quality related attributes.*

7.5.2.3 *Technical systems (e.g. machines, lines, structural production components, etc.) used for manufacturing primary packaging materials shall be verified and/or qualified/validated, in accordance with a documented risk assessment.*

7.5.2.4 *Verification and/or qualification/validation shall be performed when significant changes to the facilities, equipment and process occur which may affect the quality of the product.*

NOTE Change control of the validation process is part of the organization's change control policy.

7.5.2.5 *Where appropriate, validation of the individual product shall be carried out as agreed with the customer.*

7.5.2.6 *The results of validation shall be recorded (see 4.2.4). Validation records shall be maintained throughout the life of the equipment and process and for a period of two years beyond retirement or as agreed with the customer.*

7.5.2.7 *For software used in quality critical processes, functional tests to verify the traceability, transfer accuracy and retention of data shall be performed in sufficient number and under appropriate conditions. The system shall be checked, e.g. by entering correct and incorrect data in order to detect the traceability, transfer accuracy and retention of data or records.*

7.5.2.8 *The results of these tests and checks shall be recorded (see 4.2.4).*

7.5.2.9 *Electronic records shall be secured and protected against loss and accidental corruption and in a form that will permit regeneration; if this is not possible, hard copy prints shall be retained for a period of two years beyond equipment retirement or as agreed with the customer (see 4.2.4.1).*

NOTE For further details on data security, management and software validation, see IEC 60601-1-4, the GAMP (Good Automated Manufacturing Practice) Guide, and US/FDA Code of Federal Regulations 21, part 11.

7.5.2.10 *If any quality critical process is outsourced, the organization shall ensure that the process complies with the requirements of this International Standard.*

7.5.2.11 *If sterilization is a requirement, the organization shall establish documented procedures for the validation of sterilization processes. Sterilization processes shall be validated prior to initial use. Records of the results of sterilization process validation shall be maintained (see 4.2.4).*

See ISO 11135, ISO 11137-1 or ISO 11137-2.

7.5.2.12 *Where sterilization is a requirement, the organization shall subject the primary packaging materials to a validated sterilization process and record all the control parameters of the sterilization process. If the sterilization process is outsourced, the organization shall ensure that the process complies with the requirements of this International Standard.*

See ISO 14937.

7.5.3 Identification and traceability

ISO 9001:2008, Quality management systems — Requirements

7.5.3 Identification and traceability

Where appropriate, the organization shall identify the product by suitable means throughout product realization.

The organization shall identify the product status with respect to monitoring and measurement requirements throughout product realization.

Where traceability is a requirement, the organization shall control the unique identification of the product and maintain records (see 4.2.4).

NOTE In some industry sectors, configuration management is a means by which identification and traceability are maintained.

7.5.3.1 *The organization shall establish and maintain a system to trace all production materials from source to product realization, defining the extent and the records required based on risk assessment (see 4.2.4, 8.3 and 8.5).*

7.5.3.2 *Batch production records shall be identified with a unique batch or identification reference.*

7.5.3.3 *Records of the use of quality critical equipment shall be retained (see 4.2.4). These records shall also include cleaning and maintenance activities in sequence with the manufacturing operations. Maintenance activities shall be documented and traceable to a particular manufacturing operation or piece of equipment.*

7.5.3.4 *The organization shall establish and maintain documented procedures to ensure that primary packaging materials returned to the organization for e.g. reprocessing to specified requirements are identified and distinguished from normal production at all times.*

7.5.4 Customer property

ISO 9001:2008, Quality management systems — Requirements

7.5.4 Customer property

The organization shall exercise care with customer property while it is under the organization's control or being used by the organization. The organization shall identify, verify, protect and safeguard customer property provided for use or incorporation into the product. If any customer property is lost, damaged or otherwise found to be unsuitable for use, the organization shall report this to the customer and maintain records (see 4.2.4).

NOTE Customer property can include intellectual property and personal data.

7.5.5 Preservation of product

ISO 9001:2008, Quality management systems — Requirements

7.5.5 Preservation of product

The organization shall preserve the product during internal processing and delivery to the intended destination in order to maintain conformity to requirements. As applicable, preservation shall include identification, handling, packaging, storage and protection. Preservation shall also apply to the constituent parts of a product.

7.5.5.1 *The organization shall establish and maintain a system for the control of product with a limited shelf-life or requiring special storage conditions. Such special storage conditions shall be controlled and recorded (see 4.2.4). Shelf-lives shall be justified.*

7.5.5.2 *The product shall be clearly identified, segregated and securely stored, and protected from extraneous matter or contamination. Packaging used to produce and contain the product shall be clean and suitable. Deliveries shall be accompanied by appropriate documentation. The delivery documentation shall be batch-specific.*

7.5.5.3 *If packaging containers are reused, previous labels shall be removed or defaced. The containers shall be cleaned or verified as clean, in accordance with a documented procedure.*

7.5.5.4 *If required, any special transport or storage conditions for primary packaging materials shall be stated on the label and complied with.*

7.6 Control of monitoring and measuring equipment

ISO 9001:2008, Quality management systems — Requirements

7.6 Control of monitoring and measuring equipment

The organization shall determine the monitoring and measurement to be undertaken and the monitoring and measuring equipment needed to provide evidence of conformity of product to determined requirements.

The organization shall establish processes to ensure that monitoring and measurement can be carried out and are carried out in a manner that is consistent with the monitoring and measurement requirements.

Where necessary to ensure valid results, measuring equipment shall

a) be calibrated or verified, or both, at specified intervals, or prior to use, against measurement standards traceable to international or national measurement standards; where no such standards exist, the basis used for calibration or verification shall be recorded (see 4.2.4);

b) be adjusted or re-adjusted as necessary;

c) have identification in order to determine its calibration status;

d) be safeguarded from adjustments that would invalidate the measurement result;

e) be protected from damage and deterioration during handling, maintenance and storage.

In addition, the organization shall assess and record the validity of the previous measuring results when the equipment is found not to conform to requirements. The organization shall take appropriate action on the equipment and any product affected.

Records of the results of calibration and verification shall be maintained (see 4.2.4).

When used in the monitoring and measurement of specified requirements, the ability of computer software to satisfy the intended application shall be confirmed. This shall be undertaken prior to initial use and reconfirmed as necessary.

NOTE Confirmation of the ability of computer software to satisfy the intended application would typically include its verification and configuration management to maintain its suitability for use.

7.6.1 *There shall be regular, recorded challenge tests of automatic inspection equipment (e.g. 100 % camera inspection systems and barcode readers) to verify the continued functionality.*

7.6.2 *Production and control data related to the customer's product (excluding the organization's confidential intellectual property) shall be made available when required by the customer or customer's representative, for verification that the production process, in-process and final control and test equipment are functionally adequate.*

7.6.3 *Test equipment used in determining the acceptance of quality critical starting materials, intermediate/in-process or finished product shall be calibrated and additional qualification tests performed if appropriate.*

8 Measurement, analysis and improvement

8.1 General

ISO 9001:2008, Quality management systems — Requirements

8.1 General

The organization shall plan and implement the monitoring, measurement, analysis and improvement processes needed

a) to demonstrate conformity to product requirements,

This requirement applies to both intermediate products and primary packaging materials.

b) to ensure conformity of the quality management system, and

c) to continually improve the effectiveness of the quality management system.

This shall include determination of applicable methods, including statistical techniques, and the extent of their use.

8.2 Monitoring and measurement

8.2.1 Customer satisfaction

ISO 9001:2008, Quality management systems — Requirements

8.2.1 Customer satisfaction

As one of the measurements of the performance of the quality management system, the organization shall monitor information relating to customer perception as to whether the organization has met customer requirements. The methods for obtaining and using this information shall be determined.

NOTE Monitoring customer perception can include obtaining input from sources such as customer satisfaction surveys, customer data on delivered product quality, user opinion surveys, lost business analysis, compliments, warranty claims, dealer reports.

8.2.2 Internal audit

ISO 9001:2008, Quality management systems — Requirements

8.2.2 Internal audit

The organization shall conduct internal audits at planned intervals to determine whether the quality management system

a) conforms to the planned arrangements (see 7.1), to the requirements of this International Standard and to the quality management system requirements established by the organization, and

b) is effectively implemented and maintained.

An audit programme shall be planned, taking into consideration the status and importance of the processes and areas to be audited, as well as the results of previous audits. The audit criteria, scope, frequency and methods shall be defined. This selection of auditors and conduct of audits shall ensure objectivity and impartiality of the audit process. Auditors shall not audit their own work.

A documented procedure shall be established to define the responsibilities and requirements for planning and conducting audits, establishing records and reporting results.

Records of the audits and their results shall be maintained (see 4.2.4).

The management responsible for the area being audited shall ensure that any necessary corrections and corrective actions are taken without undue delay to eliminate detected nonconformities and their causes. Follow-up activities shall include the verification of the actions taken and the reporting of verification results (see 8.5.2).

NOTE See ISO 19011 for guidance.

8.2.3 Monitoring and measurement of processes

ISO 9001:2008, Quality management systems — Requirements

8.2.3 Monitoring and measurement of processes

The organization shall apply suitable methods for monitoring and, where applicable, measurement of the quality management system processes. These methods shall demonstrate the ability of the processes to achieve planned results. When planned results are not achieved, correction and corrective action shall be taken, as appropriate.

NOTE When determining suitable methods, it is advisable that the organization consider the type and extent of monitoring or measurement appropriate to each of its processes in relation to their impact on the conformity to product requirements and on the effectiveness of the quality management system.

The quality unit(s) shall ensure that quality critical deviations are investigated, resolved and documented.

8.2.4 Monitoring and measurement of product

ISO 9001:2008, Quality management systems — Requirements

8.2.4 Monitoring and measurement of product

The organization shall monitor and measure the characteristics of the product to verify that product requirements have been met. This shall be carried out at appropriate stages of the product realization process in accordance with the planned arrangements (see 7.1). Evidence of conformity with the acceptance criteria shall be maintained.

Records shall indicate the person(s) authorizing release of product for delivery to the customer (see 4.2.4).

The release of product and delivery of service to the customer shall not proceed until the planned arrangements (see 7.1) have been satisfactorily completed, unless otherwise approved by a relevant authority and, where applicable, by the customer.

8.2.4.1 *Investigation of OOS results*

Any out-of-specification (OOS) result shall be investigated according to a documented procedure and the outcome recorded (see 4.2.4).

8.2.4.2 *Incoming inspection and testing*

Requirements shall be established and maintained for all materials used. Incoming materials shall be inspected or otherwise verified as conforming to specified requirements.

8.2.4.3 *In-process controls*

8.2.4.3.1 *The organization shall, as required by documented procedures, inspect and test the product during processing.*

8.2.4.3.2 *Sampling procedures shall be defined to ensure that samples are representative of the process being assessed. Samples shall not be returned to the production area if removed to a separate testing location.*

8.2.4.3.3 *Additional in-process controls shall be carried out after an equipment breakdown or an unscheduled interruption which stops the process.*

8.2.4.4 *Final inspection*

If final inspection is a requirement, it shall be completed prior to batch release.

NOTE Final inspection might not include all specification parameters.

8.2.4.5 *Retained samples*

Retained samples shall be taken in accordance with the organization's and/or customer requirements.

8.2.4.6 *Batch release*

A review of batch documentation shall be performed in order to release the batch.

8.3 Control of nonconforming product

ISO 9001:2008, Quality management systems — Requirements

8.3 Control of nonconforming product

The organization shall ensure that product which does not conform to product requirements is identified and controlled to prevent its unintended use or delivery. A documented procedure shall be established to define the controls and related responsibilities and authorities for dealing with nonconforming product.

Where applicable, the organization shall deal with nonconforming product by one or more of the following ways:

a) by taking action to eliminate the detected nonconformity;

b) by authorizing its use, release or acceptance under concession by a relevant authority and, where applicable, by the customer;

c) by taking action to preclude its original intended use or application;

d) by taking action appropriate to the effects, or potential effects, of the nonconformity when nonconforming product is detected after delivery or use has started.

When nonconforming product is corrected it shall be subject to re-verification to demonstrate conformity to the requirements.

Records of the nature of nonconformities and any subsequent actions taken, including concessions obtained, shall be maintained (see 4.2.4).

8.3.1 *Nonconforming material or products shall be quarantined pending determination of corrective or other actions. When considering correction via rework or reconditioning, a risk assessment of any adverse effect of the reworking on the products shall be performed and recorded (see 4.2.4 and 7.5.1).*

8.3.2 *Rework and/or reconditioning shall be in accordance with a documented procedure that has been approved by the quality unit(s). The rework procedure shall be agreed with the customer, where this is a specified requirement.*

8.3.3 *If primary packaging material has been produced under cleanroom conditions, any rework shall be carried out under the same conditions.*

8.3.4 *Any proposal to release nonconforming product shall be via a documented concession, authorized by the customer.*

8.3.5 *Following rejection, primary packaging materials shall be disposed of or destroyed in accordance with a documented procedure.*

8.4 Analysis of data

ISO 9001:2008, Quality management systems — Requirements

8.4 Analysis of data

The organization shall determine, collect and analyse appropriate data to demonstrate the suitability and effectiveness of the quality management system and to evaluate where continual improvement of the effectiveness of the quality management system can be made. This shall include data generated as a result of monitoring and measurement and from other relevant sources.

The analysis of data shall provide information relating to

a) customer satisfaction (see 8.2.1),

b) conformity to product requirements (see 8.2.4),

c) characteristics and trends of processes and products, including opportunities for preventive action (see 8.2.3 and 8.2.4), and

d) suppliers (see 7.4).

The organization shall establish and maintain documented procedures, including requirements for the analysis of data, to identify existing or potential causes of nonconforming product or other quality problems.

8.5 Improvement

8.5.1 Continual improvement

ISO 9001:2008, Quality management systems — Requirements

8.5.1 Continual improvement

The organization shall continually improve the effectiveness of the quality management system through the use of the quality policy, quality objectives, audit results, analysis of data, corrective and preventive actions and management review.

Changes proposed as part of continual improvement shall be subject to risk management.

8.5.2 Corrective action

ISO 9001:2008, Quality management systems — Requirements

8.5.2 Corrective action

The organization shall take action to eliminate the causes of nonconformities in order to prevent recurrence. Corrective actions shall be appropriate to the effects of the nonconformities encountered.

A documented procedure shall be established to define requirements for

a) reviewing nonconformities (including customer complaints),

b) determining the causes of nonconformities,

c) evaluating the need for action to ensure that nonconformities do not recur,

d) determining and implementing action needed,

e) records of the results of action taken (see 4.2.4), and

f) reviewing the effectiveness of the corrective action taken.

8.5.2.1 *The organization shall investigate all customer complaints in a timely manner and communicate identified corrective action to all production and production-related sites. Action(s) shall be implemented as soon as practical and to an agreed timetable; records of investigation shall be maintained (see 4.2.4).*

8.5.2.2 *Customer complaints not followed by corrective and/or preventive action shall be justified and also recorded (see 4.2.4).*

8.5.3 Preventive action

ISO 9001:2008, Quality management systems — Requirements

8.5.3 Preventive action

The organization shall determine action to eliminate the causes of potential nonconformities in order to prevent their occurrence. Preventive actions shall be appropriate to the effects of the potential problems.

A documented procedure shall be established to define requirements for

a) determining potential nonconformities and their causes,

b) evaluating the need for action to prevent occurrence of nonconformities,

c) determining and implementing action needed,

d) records of results of action taken (see 4.2.4), and

e) reviewing the effectiveness of the preventive action taken.

Annex A
(normative)

GMP requirements for printed primary packaging materials

A.1 Print impression media

A.1.1 General

All print impression media shall be

a) clearly and uniquely identified such that it is traceable to the origination material,

b) produced from, and traceable to, the master origination material held by the customer,

c) verified against the customer approved hard copy or electronic data and recorded (see 4.2.4), and

d) stored in a secure area with a defined system for authorized issue and return to store.

A.1.2 Matched plates

Where more than one printing plate is required, there shall be a documented system for ensuring that all plates within the set are used. Where a set of plates contains the generic design for several jobs, each individual plate within the set shall be clearly, uniquely identified and documented.

A.1.3 Copy/design change

Where a design requires several plates and some of them are to be replaced because of a copy/design change, there shall be a documented procedure to allow for the replacement of the affected plate(s) and the retention of the other media within the set. The original plates shall be subject to a procedure that allows re-identification.

A.1.4 Verification

A.1.4.1 General

Verification of the design on print impression media shall be carried out during the printing machine make-ready and before the approval to run the product is given.

A.1.4.2 Quarantine and destruction

The organization shall have

a) a documented procedure which ensures that origination and print media, for a design undergoing revision, are subject to formal quarantine, and

b) a documented system detailing the method for disposal of the unwanted origination and print impression media; such items shall be rendered unusable and disposed of in a controlled and secure manner.

A.2 Print and conversion processes

A.2.1 Print machine set-up (make-ready)

A.2.1.1 *Initial print make-ready shall be performed using unprinted components or material.*

A.2.1.2 *Make-ready for subsequent processes may use material from the initial print process of the same batch.*

A.2.1.3 *Initial make-ready material may be reused during the make-ready process in order to achieve correct colour.*

A.2.1.4 *Material used for make-ready shall be segregated and then disposed of as production waste.*

A.2.2 Changeover systems

Changeover systems that are designed to reduce make-ready time (e.g. automated plate changing), and which do not permit a total line clearance, shall be subject to a documented risk assessment and operated with controls to ensure product security. All print media from the previous job shall be removed from the line prior to formal approval of the print run being given. All controls shall be recorded (see 4.2.4).

A.2.3 Retained samples

A.2.3.1 *All in-process printed samples which are to be retained shall be clearly identified and securely stored.*

A.2.3.2 *Samples used for other purposes (e.g. administration/sales) shall be voided if they leave the control of the organization.*

A.2.4 Replacement print media

A.2.4.1 *During a production run, if replacement plates are made from an existing fixed approved source (e.g. negatives, or using computer-to-plate technology from an existing stepped image), the job may be continued after a new "first off" check has been carried out.*

A.2.4.2 *During a production run, if plates are created from a new source (e.g. re-stepping a "one-up" image), the existing job shall be lifted, the replacement plates shall be treated as new origination. Subsequent production shall be treated as a new batch. The introduction of all replacement print media shall be recorded (see 4.2.4).*

A.2.5 Gang printing

Gang printing (the process of printing more than one design on a substrate at one production run) is not permitted because of the risk of cross-contamination

A.2.6 Batched production and stock holding

A.2.6.1 *Batched production and holding of product in stock shall only be practised if contractually agreed.*

A.2.6.2 *The organization shall control the storage to ensure security and integrity of the product and maintain its traceability back to manufacture and the materials used.*

A.2.7 Digital printing

A.2.7.1 *The flexible capabilities of digital printing introduce new activities, which shall be controlled and documented to ensure the accuracy and security of the printed products.*

A.2.7.2 *The use of digital printing and any special requirements for the product shall be agreed with the customer.*

A.2.7.3 *The organization shall establish a secure file access system, which is designed to prevent unintentional use of incorrect origination files.*

A.2.7.4 *Unless alternative security is designed, the controlling computer within the digital printing machine shall have only the specific origination file in its memory for the current print run, and removal of this file shall form part of documented line clearance.*

A.2.7.5 *Operational settings to achieve acceptable colours shall be established through a formal process and recorded (see 4.2.4).*

A.3 Security barcode systems

A.3.1 General

To ensure the security of the product and prevent cross-contamination, security barcodes may be included in the design of printed packaging materials for verification either by the organization during manufacture and/or by the customer during the packaging operation.

Where agreed as part of the contract, the organization may add its own identification codes to the product design.

Where the organization is responsible for specifying the security barcode, each colour of the design should be included in the barcode. For all barcodes, if a colour is not compatible with the requirements of the scanning equipment, the customer shall be notified of this.

A.3.2 Verification methods/equipment

A.3.2.1 *Where practical, every security barcoded item shall be verified by on-line scanning equipment to ensure that the codes are readable and that the correct product is being produced. Scanning of security barcodes should be carried out during the last feasible production process.*

A.3.2.2 *The scanning equipment software/control configuration shall be loaded from an independent source (e.g. specification or approved proof). Once a code is entered and checked, the scanning equipment shall be effectively locked (e.g. use of mechanical lock or password protection) to prevent unauthorized access.*

A.3.2.3 *There shall be an effective system for rejecting any product that fails the scanning process. Any product rejected by the on-line scanning system shall be inspected to determine the cause of rejection and the rejected components subsequently scrapped. These findings shall be recorded and reviewed prior to product release.*

A.3.2.4 *The on-line scanning equipment and its associated reject mechanism shall be subjected to a challenge test during production to verify whether its operation is effective in detecting and removing incorrectly barcoded material. Such monitoring shall take place at the start of the process, at regular intervals, and be recorded (see 4.2.4).*

A.3.2.5 *Any product produced where electronic scanning is specified, but has not been performed, shall be properly authorized and recorded in the quality records. The customer shall be notified and documented approval obtained before product release.*

A.3.2.6 *For reel-fed multi-lane production, all lanes should be subject to barcode verification. Where this cannot be performed, and in agreement with the customer, one lane only may be verified.*

A.3.2.7 *Off-line measurements and/or verification of sample barcodes from all lanes shall be carried out.*

A.3.3 “Point of sale” barcodes

Where “point of sale” barcodes (EAN, Code 39, PZN, etc.) are incorporated into the design, a documented sample verification check shall be carried out during the production process.

A.3.4 Reel materials and products

A.3.4.1 *Unless otherwise specified by the customer, splices shall be*

a) made using a brightly coloured adhesive tape on both sides of the web, and

b) checked either side of the splice to ensure that identical materials are joined and in register.

A limit on the maximum number of splices may be specified.

A.3.4.2 *The quantity of material (length, weight or numerical) produced on each reel shall be determined within accuracy limits agreed with the customer and recorded on the reel.*

A.3.4.3 *The batch identity, reel number and production date shall be recorded on the inner face of the core for each individual reel.*

A.3.4.4 *To prevent cross-contamination, the web shall be run to plain material at the end of the run to ensure that no printed material remains in the printing equipment.*

A.3.4.5 *Where it is necessary to leave printed material in the converting equipment due to the difficulty in carrying out re-webbing (e.g. slitters), there shall be a formal documented procedure for removal and disposal of the material used to pull the new design through the machine.*

A.3.4.6 *If material with missing print can be produced as a consequence of the design or operation of the printing equipment, the organization shall have a secure system for the detection, removal and segregation of product produced with missing colours or text.*

Annex B
(informative)

Guidance on verification and validation requirements for primary packaging materials

B.1 General

This informative annex describes the approach when validation is required, as it is assumed that some form of verification will always be required.

The guidance relates to the requirements for validation given in 7.5.2 and 7.5.2.1, and the requirements for design and development given in 7.3.

Items which may require qualification/validation (where risk analysis has determined that verification alone is not sufficient) include

— *technical systems such as machines and lines for production of primary packaging materials,*

— *test equipment used for determining the acceptance of quality critical starting materials, intermediate/in-process or finished product, and*

— *validation of individual product, where appropriate or as agreed with the customer.*

The aim of validation is to demonstrate consistent manufacturing and packaging of products in accordance with the product requirements. It is a means of establishing documented evidence that the equipment and processes used to produce and test the primary packaging material will consistently produce a product that meets a pre-determined specification.

Validation is required when either the organization has determined or the customer has agreed that verification alone is not sufficient. If only the verification approach is used there should be a documentation set which includes the acceptance criteria and results of site acceptance testing (SAT) (see B.16), and which specifies the requirements for monitoring and measurement during routine production.

B.2 Guidance considerations

B.2.1 General

In compliance with 7.5.2, formal qualification/validation is only required for defined quality critical parameters which cannot be verified by routine monitoring or measurement. This clause provides guidance and consideration where validation might be deemed necessary.

Calibration is independent of validation.

B.2.2 Considerations prior to verification/qualification/validation

Prior to verification, qualification or validation of the process required to manufacture primary packaging material, consideration should be given to the following:

— *the material composition and specification;*

— *the equipment on which it is to be produced and packed;*

— *identification of roles and agreed responsibilities (organization and customer);*

— *the potential impact of the primary packaging material on the medicinal product and patient safety;*

— *definition of critical process parameters;*

— *training requirements (operators, quality personnel, engineers, etc.);*

— *standard operating procedures to provide detail on how to produce/operate and clean the equipment.*

B.3 Software verification/validation

Software may be verified by so-called functional tests. Software validation is not a prerequisite for the manufacture of primary packaging materials unless specifically designated otherwise.

B.4 Functional tests

For software used in quality critical processes, functional tests for the verification of traceability, transfer accuracy, processing and retention of data should be performed in sufficient number and under appropriate conditions. The system should be checked, e.g. by entering correct and incorrect data, in order to detect the traceability, transfer accuracy and retention of data and records. The results of these tests and checks should be recorded.

Double-checks on critical steps and parameters should be performed during functional test runs.

B.5 Change control

Formal, documented change control should be part of the validation process, from the end of the design qualification (see B.13) and throughout the lifetime of the equipment. Change control of verification steps or validation processes should be part of the organization's change control policy.

B.6 Follow-up

Action should be taken to complete any outstanding actions, e.g. snag lists following operational qualification (see B.15) and performance qualification (see B.17).

All actions taken should be documented.

B.7 Maintenance of the validated status

The validated status of equipment and process should be maintained. Any changes, however minor, should be assessed for impact on the validation status of equipment or product and, if necessary, a confirmation exercise equivalent to one performance qualification (B.17) batch conducted.

Changes/improvements to validation procedures should also be assessed to determine if re-validation is required.

B.8 Validation approach

B.8.1 Prospective validation approach

Validation should occur prior to commercial production and follow the prospective validation approach. See also B.21 for alternative approaches to validation.

A flow-chart showing the sequence of the typical validation steps is attached as Figure B.1.

B.8.2 Roles and responsibilities

Figure B.1 depicts potential areas of responsibility. Within these functions, individuals with responsibility for conducting the verification or validation processes and authorizing the results should be identified prior to the commencement of work.

Any product release decisions should be the responsibility of the quality unit.

B.8.3 Planning

B.8.3.1 General

All stages of the verification and/or validation process should be planned and documented. A decision on the type of documentation required should be taken at the start of the process, e.g. where verification is the agreed approach, a user requirement specification may be extended to detail the processes required to ensure verification.

The purpose of validation is to determine that the requirements of the user are met, and these should therefore be clearly specified.

B.8.3.2 Validation master plan (VMP)

The overall validation approach and plan should be described in a validation master plan (VMP).

This is a document that describes how the validation of the equipment and/or process will be accomplished, lists the key responsibilities and order of execution of the activities. The plan sets out the validation approach, focusing on the quality critical aspects of the equipment and/or process.

It should usually include the following elements:

- *validation plan;*
- *organizational structure of validation activities — roles and responsibilities;*
- *summary of facilities, systems, equipment and process;*
- *documentation format — level of documentation required;*
- *planning and scheduling;*
- *references to existing documents, if applicable;*
- *change control.*

Where a range of products or equipment which, following risk analysis, are considered equivalent require validation, a bracketing and/or matrix validation approach may be appropriate. The justification for this decision should be documented in the validation plan. There should be sufficient process and product knowledge on which to base a sound rationale for use of a matrix and/or bracketing approach. Bracketing

means testing only the extremes of identified parameters. The matrix approach may use "design of experiments" to reduce the number of formal validation batches required.

B.9 Risk analysis

Risk analysis is an inherent part of the decision-making process and may be used to determine whether verification and/or validation is required. It may also be used during design qualification to determine any potential hazards for either operators or the environment. These include machine access (guarding), material flow, exposure to lasers, etc. Figure B.1 illustrates two stages where risk analysis is required.

B.10 User requirement specification (URS)

The planning stage should include the development of a user requirement specification (URS). A URS is an approved document that states each functional, operational and/or technical attribute of the equipment or process required to produce the desired material. This may include consideration for equipment layout with sufficient space for material flow and operators, availability of spare parts, and ease of access for cleaning and line clearance. Alternatively, this information may be provided in other documentation.

B.11 Contract specification/factory acceptance test (FAT)

This is a legal documented agreement that should be reached between the organization and supplier, signed by both parties, agreeing terms and conditions for what is to be supplied. If factory acceptance tests (FAT) are required, the document should specify the tests required and where these tests should be performed and by whom.

B.12 Validation stages

Various options exist for the approach to design qualification (see B.13)/installation qualification (see B.14)/operational qualification (see B.15)/site acceptance test (see B.16)/performance qualification (see B.17) and risk analysis by supplier and/or organization. This work should be documented, e.g. the organization might utilize the supplier's expertise during trials/optimization work/SAT.

Following planning for validation, the qualification process may be initiated. Qualification provides the proof that the product can be produced to the required standard repeatedly (see B.16).

B.13 Design qualification (DQ)

This is the process that verifies the suitability of the design. This may include appropriate risk analysis, user requirement specifications, contract specifications (may be a single document), factory acceptance tests [(FAT) to determine that the equipment is ready to be dispatched from the supplier to the organization] and any development/optimization trials prior to the site acceptance test (SAT) (see B.16).

DQ is not necessary for standardized non-customized equipment.

FAT may include consideration for environmental control, i.e. heat, noise, light, dust.

B.14 Installation qualification (IQ)

This is approved documented evidence that the equipment is installed according to written and approved specifications and drawings and that it has all the features installed as per the design specification, is calibrated, where appropriate, and has all operating manuals in place.

B.15 Operational qualification (OQ)

This is the performance of tests based on knowledge of the process and systems to ensure the operation is doing what it is expected to do at the upper and lower ends of the required operating limits, where appropriate, taking into account the variation in all raw materials and the environment in which the equipment is installed.

The test process and results should be formally documented and approved and there may be separate documents for the test plan/test protocol (see B.19.3.2), test report/test record (see B.19.3.4) and conclusion (see B.19.3.5).

OQ should finalize procedures for calibration, operating [including nature and frequency of in-process controls (IPC)], cleaning, operator training and preventive maintenance.

For simple equipment, a single document may cover both test plan/test protocol (see B.19.3.2) and test report/test record (see B.19.3.4), in which case the acceptance criteria should be defined within the document.

B.16 Site acceptance test (SAT)

Site acceptance tests may verify that IQ/OQ has been completed successfully by means of a simulated production run using actual production materials. The output should be monitored and measured and the results used to determine if performance qualification is required. SAT may be equivalent to one performance qualification run.

SAT may also be required for test equipment including verification that the equipment has been calibrated and produces consistent results.

B.17 Performance qualification (PQ)

PQ uses challenge tests of the overall line performance to ensure that it can produce consistently at the quality standard required. PQ testing uses production materials to verify that the process is robust and the primary packaging material can be consistently produced under routine operating conditions. The test process and results of a minimum of three subsequent production batches are formally documented and approved.

An exception to using three subsequent batches may be made where the production process is lengthy, for example a single batch of material may require several weeks of continuous production. In this case, PQ may be conducted on three sub-batches of a minimum of one day's duration each.

B.18 Product validation

Product validation is optional, either after an internal decision of the organization or at the request of the customer (see Figure B.1).

In the case of special requirements, it is recommended to validate the quality critical process steps for an individual primary packaging material. The critical process steps should be tested with critical parameters selected by a risk assessment. Product validation should include machine and process ability and qualification of 100 % online controls.

It is generally considered acceptable that the number of consecutive batches/runs within the finally agreed parameters would constitute a validation of the process (see EU GMP Guide, Annex 15).

B.19 Documentation for the verification and validation processes

B.19.1 General

It is recommended that the approach to, and each stage of, the verification/validation process and the results be recorded (see 4.2.4).

B.19.2 Verification

A single document may be used to document the factory acceptance test (FAT) and/or site acceptance test (SAT). This may include all or some of the following:

— *history of development or prior testing/verification/validation;*

— *justification for the approach taken;*

— *acceptance criteria*;

— *tests to be performed;*

— *test results;*

— *assessment of test results and conclusions;*

— *follow-up;*

— *change control;*

— *authorization.*

B.19.3 Validation

B.19.3.1 Scope of documentation

The basic documentation for validation should consist of the following:

— *risk analysis;*

— *test plan/protocol (qualification plan/protocol);*

— *test report(s) (test record);*

— *conclusion and approval.*

B.19.3.2 Test plan/test protocol (qualification plan/qualification protocol)

This consists of one or more documents detailing the development and performance tests, including qualification tests. These documents should include the following:

— *key steps deemed quality critical;*

— *tests to be conducted and the methods to be employed;*

— *acceptance criteria;*

— *a formal sign-off for review and approval.*