BS EN ISO 15378:2015

BSI Standards Publication

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

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National foreword

This British Standard is the UK implementation of EN ISO 15378:2015. It supersedes BS EN ISO 15378:2011 which is withdrawn.

The UK participation in its preparation was entrusted to Technical Committee CH/212, IVDs.

A list of organizations represented on this committee can be obtained on request to its secretary.

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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) (ISO 15378:2015)

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) (ISO 15378:2015)

Primärpackmittel für Arzneimittel - Besondere Anforderungen für die Anwendung von ISO 9001:2008 entsprechend der Guten Herstellungspraxis (GMP) (ISO 15378:2015)

This European Standard was approved by CEN on 3 October 2015.

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EUROPEAN COMMITTEE FOR STANDARDIZATION
COMITÉ EUROPÉEN DE NORMALISATION
EUROPÄISCHES KOMITEE FÜR NORMUNG

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Ref. No. EN ISO 15378:2015 E

European foreword

This document (EN ISO 15378:2015) has been prepared by Technical Committee ISO/TC 76 "Transfusion, infusion and injection, and blood processing equipment for medical and pharmaceutical use".

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by May 2016, and conflicting national standards shall be withdrawn at the latest by May 2016.

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

This document supersedes EN ISO 15378:2011.

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Endorsement notice

The text of ISO 15378:2015 has been approved by CEN as EN ISO 15378:2015 without any modification.

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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.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary information

The committee responsible for this document is ISO/TC 76, *Transfusion, infusion and injection, and blood processing equipment for medical and pharmaceutical use*.

This third edition cancels and replaces the second edition (ISO 15378:2011), which has been technically revised to

— include requirements on risk management and replace the former guidance on risk management by references to relevant standards and guidelines,

— extensively revise the guidance on verification, qualification and validation requirements for primary packaging materials, and

— amend the requirements on infrastructure, work environment, maintenance and cleaning activities, customer communication, control of production and service provision and batch release.

Introduction

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

— *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.

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.

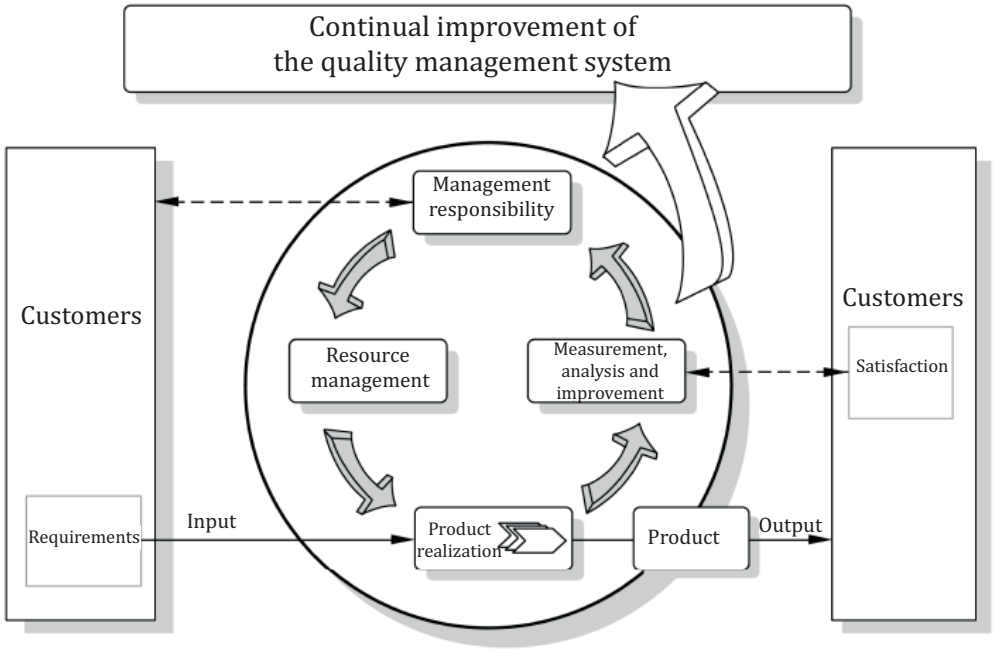
NOTE In addition, the methodology known as "Plan-Do-Check-Act" (PDCA) can be applied to all processes. PDCA can be briefly described as follows.

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



Key

value-adding activities

information flow

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

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.

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.

NOTE ISO 9001:2008, Annex A is not included in this International Standard.

INTERNATIONAL STANDARD **ISO 15378:2015(E)**

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 documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. 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 14698-1, *Cleanrooms and associated controlled environments — Biocontamination control — Part 1: General principles and methods*

ISO 14698-2, *Cleanrooms and associated controlled environments — Biocontamination control — Part 2: Evaluation and interpretation of biocontamination data*

3 Terms and definitions

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

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.[1)]

1) The systematic used for the grouping of the terms and definitions in this International Standard is based on that used in ISO 9000.

3.1 *Terms relating to quality*

3.1.1
customer complaint
information provided by a customer about deficiencies and/or nonconformities

Note 1 to entry: *The information can be verbally communicated or written.*

Note 2 to entry: *The subject of a complaint can include* ***primary packaging material*** *(3.4.18.1) quality, quantity or supply.*

3.2 *Terms relating to management*

3.2.1
Good Manufacturing Practice
GMP
quality control *(3.2.2) and quality assurance applied in* ***manufacturing*** *(3.4.15)*

Note 1 to entry: to entry: *For the definitions of* ***quality control*** *(3.2.2) and quality assurance, see* ISO 9000:2005, 3.2.10 and 3.2.11.

Note 2 to entry: *Requirements for* ***Good Manufacturing Practice*** *in the pharmaceutical industry are specified in a quality assurance standard. See Reference [32].*

Note 3 to entry: ***Good Manufacturing Practice (GMP)*** *for* ***primary packaging material*** *(3.4.18.1) requires, in addition to suitable provision of personnel, premises and equipment, a quality management system that includes controls for incoming* ***starting materials*** *(3.4.28), manufacture, corresponding documentation, factory hygiene,* ***final inspection*** *(3.8.5), records of distribution, processing of complaints and self-inspection.*

Note 4 to entry: ***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*** *(3.3.1) take account of current* ***GMP*** *within their continual improvement programmes.*

3.2.2
quality control
part of quality management focused on fulfilling quality requirements

Note 1 to entry: ***Quality control*** *includes checking or testing that* ***specifications*** *(3.7.3) are met.*

[SOURCE: ISO 9000:2005, 3.2.10*]*

3.3 *Terms relating to organization*

3.3.1
organization
group of people and facilities with an arrangement of responsibilities, authorities and relationships

Note 1 to entry: *In this International Standard, the* ***organization*** *is the company* ***manufacturing*** *(3.4.15) the* ***primary packaging material*** *(3.4.18.1).*

[SOURCE: ISO 9000:2005, 3.3.1 *modified by adding note 1 to entry]*

3.3.2
outsourcing
provision of all or part of a process by another ***organization*** *(3.3.1)*

Note 1 to entry: ***Outsourcing*** *is often referred to as subcontracting.*

3.3.3
quality unit
organizational unit which fulfils both quality assurance (QA) and ***quality control*** *(QC) (3.2.2) responsibilities*

Note 1 to entry: *The* ***quality unit(s)*** *can consist of separate QA and QC units or of a single individual (or group), depending upon the size and structure of the* ***organization*** *(3.3.1).*

3.4 *Terms relating to processes and product*

3.4.1
air-lock
enclosed space to control air-flow

Note 1 to entry: *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.*

3.4.2
assembly
fitting together of ***primary packaging materials*** *(3.4.18.1) and/or components*

Note 1 to entry: *Examples can include pipette assemblies for filling, prepared components of injection systems or positioning of needle shields on prefillable syringes.*

3.4.3
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

[SOURCE: ISO 14644-1:1999, 2.1.1]

3.4.4
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

Note 1 to entry: *This zone may be open or enclosed and may or may not be located within a* ***cleanroom*** *(3.4.3).*

[SOURCE: ISO 14644-1:1999, 2.1.2*]*

3.4.5
contamination
introduction of any unwanted material into the ***primary packaging material*** *(3.4.18.1)*

Note 1 to entry: *A* ***finished product*** *(3.4.11) can be contaminated by physical (particulate), chemical or biological (bio- and endotoxin burden) action.*

Note 2 to entry: ***Contamination*** *can occur e.g. during* ***production*** *(3.4.20), for packaging, storage and/or distribution from contaminated air systems, personnel, sampling equipment, materials, premises or containers.*

3.4.6
controlled area
controlled environment
area or environment constructed and operated to control the possible introduction of potential contaminants

3.4.7
cross-contamination
mix-up
contamination *(3.4.5) of a material or of a product with another material or product*

Note 1 to entry: ***Cross-contamination*** *can also be referred to as admixture.*

Note 2 to entry: *See Reference [31].*

3.4.8
date of manufacture
date on which one of the first stages in the process of manufacture of the ***primary packaging material*** *(3.4.18.1), or the packaging, or the final release, occurs, and which can be subject to customer agreement*

3.4.9
documented procedure
procedure that is established, documented, authorized, implemented and maintained

3.4.10
expiration date
expected suitable use limit

Note 1 to entry: *See also definition* ***shelf-life*** *(3.4.26).*

Note 2 to entry: *This is typically the period during which a* ***primary packaging material*** *(3.4.18.1) is expected to remain suitable for use if stored under defined conditions and after which it should not be used.*

3.4.11
finished product
primary packaging material *(3.4.18.1) which has completed all stages of* ***production*** *(3.4.20)*

3.4.12
homogeneity
uniformity of characteristics and their values throughout a defined quantity of material

Note 1 to entry: ***Homogeneity*** *can include uniformity of materials or certain characteristics of materials of special significance.*

3.4.13
intermediate product
primary packaging material *(3.4.18.1) which has completed some but not all production stages*

Note 1 to entry: *An* ***intermediate product*** *needs further processing before it becomes a* ***finished product*** *(3.4.11).*

3.4.14
line clearance
removal (line purge) of everything associated with the prior production run

Note 1 to entry: *Typically,* ***line clearance*** *is done prior to a production run to prevent any error and* ***cross-contamination*** *(3.4.7). Typically, it is required that a production facility (line) and its associated* ***working area*** *(3.4.31) 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.*

3.4.15
manufacturing
all operations including purchasing and receipt of materials to ***production*** *(3.4.20), packaging, labelling,* ***quality control*** *(3.2.2), release, storage, distribution of products and the related controls*

3.4.16
medicinal product
any substance or combination of substances presented for treating or preventing disease in human beings or animals

Note 1 to entry: *Any substance or combination of substances that can 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 to entry: *See Reference [31].*

Note 3 to entry: ***Medicinal products*** *can also be referred to as pharmaceutical or drug products, including clinical trial products.*

3.4.17
origination
artwork
all preparative activities prior to print

Note 1 to entry: *These include concept, design, graphics, reprographics, film, plate making, silk screens and digital files and masters.*

3.4.18 Packaging materials

3.4.18.1
primary packaging materials
materials used in pharmaceutical packaging which will contain, seal or be used for dose application of a ***medicinal product*** *(3.4.16) and which will have direct contact with the* ***medicinal product***

3.4.18.2
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

3.4.19
process aids
material used to facilitate process realization

Note 1 to entry: *The material is not included in the product* ***specification*** *(3.7.3) and can be removed at or before the final processing stage.*

EXAMPLE *Mould release agents, compressed air, rolling lubricants.*

3.4.20
production
processes resulting in ***primary packaging material*** *(3.4.18.1)*

Note 1 to entry: *The processes form the full production cycle, from receipt of* ***starting materials*** *(3.4.28) through processing and packaging, to completion as a* ***finished product*** *(3.4.11).*

3.4.21
quality critical
parameter affecting ***primary packaging material*** *(3.4.18.1) quality*

Note 1 to entry: *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.*

3.4.22
quarantine
status of materials or products isolated pending a decision on their subsequent approval or rejection

Note 1 to entry: *Quarantined material is typically isolated by physical or other effective means.*

3.4.23
realization
generic term which covers all processes required to achieve the desired output from design to product delivery

3.4.24
reconditioning
processing or reprocessing ***primary packaging material*** *(3.4.18.1) to meet* ***specification*** *(3.7.3) requirements*

3.4.25
reprocessing
repeating part of a production process

Note 1 to entry: *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.*

3.4.26
shelf-life
period during which a ***primary packaging material*** *(3.4.18.1) is expected to comply with the requirements (specifications) if stored under defined conditions and after which it should not be used*

Note 1 to entry: *See also* ***expiration date*** *(3.4.10).*

3.4.27
standard operating procedure
SOP
authorized, ***documented procedure*** *(3.4.9) or set of procedures, work instructions and test instructions for* ***production*** *(3.4.20) and control*

3.4.28
starting material
raw material/components/substances used to produce ***primary packaging materials*** *(3.4.18.1)*

3.4.29
sterile
state of being free from viable microorganisms

[SOURCE: ISO 14937:2009, 3.26]

3.4.30
surface treatment
process to improve ***primary packaging material*** *(3.4.18.1) surface*

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

3.4.31
working area
defined area where origination, production, packaging, test or inspection operations are carried out and where such activity will usually be subject to a line-clearance

Note 1 to entry: *These areas are physically defined by the use of barriers, floor marking or similar means of definition, and can contain equipment, e.g. production machinery, test equipment, computers, work benches, proofing equipment.*

3.5 *Terms relating to characteristics*

3.5.1
batch
lot
defined quantity of ***primary packaging material*** *(3.4.18.1) manufactured in one process or series of processes intended to have uniform characteristics with consistent, homogeneous quality*

Note 1 to entry: *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 to entry: *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.*

3.5.2
traceability
ability to trace the history, application or location of that which is under consideration

Note 1 to entry: *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 to entry: *In the field of metrology, the definition in* ISO/IEC Guide 99:2007, 2.41 *(third edition of VIM), is the accepted definition.*

[SOURCE: ISO 9000:2005, 3.5.4 *modified by updating the reference in Note 2 to entry]*

3.6 *Terms relating to conformity*

3.6.1
approved
confirmed conformity status

Note 1 to entry: *Conformity can be confirmed for any stage of the process [****starting materials*** *(3.4.28),* ***process aids*** *(3.4.19), packaging material or* ***finished product*** *(3.4.11)].*

3.6.2
batch release
decision to release the ***batch*** *(3.5.1) for sale or supply, following a formal review of the* ***batch document*** *(3.7.1) performed by the* ***quality unit*** *(3.3.3) or a person authorized by the* ***quality unit(s)***

3.6.3
deviation
departure from an ***approved*** *(3.6.1)* ***standard operating procedure (SOP)*** *(3.4.27) or established standard*

3.6.4
out of specification
OOS
test results that do not comply with the ***specification*** *(3.7.3)*

3.6.5
rejected
status of ***starting materials*** *(3.4.28),* ***process aids*** *(3.4.19),* ***intermediate products*** *(3.4.13) or* ***finished products*** *(3.4.11) whose test results do not comply with one or more of the requirements of the* ***specification*** *(3.7.3), and which have been deemed, usually by the* ***quality unit (s)*** *(3.3.3), as not suitable for use*

3.6.6
rejection
process whereby ***starting materials*** *(3.4.28),* ***process aids*** *(3.4.19),* ***intermediate products*** *(3.4.13) or* ***finished products*** *(3.4.11) which have been deemed, usually by the* ***quality unit(s)*** *(3.3.3), as not suitable for use*

3.6.7
retained samples
materials or ***finished products*** *(3.4.11) stored for future reference*

Note 1 to entry: *These samples are generally taken in a sufficient amount and stored under recommended conditions for reference during a defined period of time.*

3.6.8
return
process for sending back ***primary packaging material (s)*** *(3.4.18.1) to the* ***organization*** *(3.3.1)*

3.6.9
rework
action on a nonconforming product to make it conform to the requirements

Note 1 to entry: *Sorting can be considered to be* ***rework***.

[SOURCE: ISO 9000:2005, 3.6.7, *modified by adding note 1 to entry]*

3.7 *Terms relating to documentation*

3.7.1
batch document
batch record
documents and records that provide a history of the ***batch*** *(3.5.1), including information relating to its production and control, and which facilitate its* ***traceability*** *(3.5.2)*

3.7.2
batch number
lot number
unique identifier to identify a ***batch*** *(3.5.1)*

Note 1 to entry: *A* ***batch number*** *can be a combination of numbers, letters and/or symbols which identifies a* ***batch*** *(3.5.1) (or lot) and from which the production and distribution history can be determined.*

3.7.3
specification
document stating requirements

[SOURCE: ISO 9000:2005, 3.7.3]

3.7.4
user requirement specification
URS
approved *(3.6.1) document that states the product* ***specifications*** *(3.7.3) of the material produced on this equipment as well as functional, operational and/or technical aspects of the equipment or process required to produce the desired product*

3.8 *Terms relating to examination*

3.8.1
automated inspection
conformity evaluation performed by inspection equipment without manual intervention

Note 1 to entry: *The inspection equipment can include optoelectronics (cameras), laser systems, ultrasonics and their associated data processing functions or others.*

3.8.2
calibration
process of checking or adjusting (by comparison with a reference standard) the accuracy of a measuring instrument

Note 1 to entry: ***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.*

3.8.3
change control
documented control of changes

Note 1 to entry: *Changes can include, for example, changes in raw materials,* ***specifications*** *(3.7.3), facilities, equipment, production processes and test methods.*

3.8.4
double-check
*documented **verification** (3.8.13) of an activity, result or record by a second person or system*

Note 1 to entry: *A second in-process control check signature, **production** (3.4.20) and quality records for a **batch** (3.5.1) signed by a second person or electronic checks can be part of this verification process. Typically, **double-checks** are signed by a second person.*

3.8.5
final inspection
*tests carried out on the **finished product** (3.4.11) to determine compliance with the **specification** (3.7.3)*

3.8.6
in-process control
*actions taken during the production process to test product conformity to its **specification** (3.7.3)*

Note 1 to entry: *Monitoring processes and adjusting the means of **production** (3.4.20) can be necessary to meet product requirements.*

Note 2 to entry: *The control of the environment or equipment can also be regarded as a part of **in-process control**.*

3.8.7
installational qualification
IQ
*process of obtaining and documenting evidence that equipment has been provided and installed in accordance with its **specification** (3.7.3)*

[SOURCE: ISO/TS 11139:2006, 2.22]

3.8.8
operational qualification
OQ
process of obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures

[SOURCE: ISO/TS 11139:2006, 2.27]

3.8.9
performance qualification
PQ
***verification** (3.8.13) that the proposed **specification** (3.7.3) for the facility, equipment or system is suitable for the intended use*

[SOURCE: ISO/TS 11139:2006, 2.30]

3.8.10
qualification process
qualification
process to demonstrate the ability to fulfil specified requirements

Note 1 to entry: *The term "qualified" is used to designate the corresponding status.*

Note 2 to entry: *Qualification comprise design qualification (DQ), **installational qualification** (IQ) (3.8.7), **operational qualification** (OQ) (3.8.8) and could include **performance qualification** (PQ) (3.8.9) as well as re-qualification.*

Note 3 to entry: *Qualification can be applied to facilities, equipment and utilities.*

[SOURCE: ISO 9000:2005, 3.8.6, *modified by adding the term qualification and by adding note 1 and note 2 to entry]*

3.8.11
reconciliation
*comparison between the amount of **finished product** (3.4.11) theoretically and actually produced or used, making allowance for normal variation*

Note 1 to entry: *The comparison considers waste, samples or other losses inherent in the process.*

3.8.12
validation
confirmation, through the provision of objective evidence that the requirements for a specific intended use or application have been fulfilled

Note 1 to entry: *The term "validated" is used to designate the corresponding status.*

Note 2 to entry: ***Validation** can be applied to processes, products and software.*

[SOURCE: ISO 9000:2005, 3.8.5, *modified by adding note 2 to entry]*

3.8.13
verification
confirmation, through the provision of objective evidence that specified requirements have been fulfilled

Note 1 to entry: *The term "verified" is used to designate the corresponding status.*

Note 2 to entry: *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.*

Note 3 to entry: *In this International Standard, the term **verification** is used to ensure manufacturing systems are properly installed and operating correctly; alternatively this could be done by IQ and OQ.*

[SOURCE: ISO 9000:2005, 3.8.4, *modified by adding note 3 to entry]*

3.9 *Terms relating to risk management*

3.9.1
risk analysis
process to comprehend the nature of risk and to determine the level of risk

Note 1 to entry: ***Risk analysis** provides the basis for **risk evaluation** (3.9.3) and decisions about risk treatment.*

Note 2 to entry: ***Risk analysis** includes risk estimation.*

[SOURCE: ISO Guide 73:2009, 3.6.1*]*

3.9.2
risk assessment
*overall process of **risk identification** (3.9.4), **risk analysis** (3.9.1) and **risk evaluation** (3.9.3)*

[SOURCE: ISO Guide 73:2009, 3.4.1]

3.9.3
risk evaluation
*process of comparing the results of **risk analysis** (3.9.1) with risk criteria to determine whether the risk and/or its magnitude is acceptable or tolerable*

Note 1 to entry: ***Risk evaluation** assists in the decision about risk treatment.*

[SOURCE: ISO Guide 73:2009, 3.7.1*]*

3.9.4
risk identification
process of finding, recognizing and describing risks

Note 1 to entry: ***Risk identification*** *involves the identification of risk sources, events, their causes and their potential consequences.*

Note 2 to entry: ***Risk identification*** *can involve historical data, theoretical analysis, informed and expert opinions, and stakeholder's needs.*

[SOURCE: ISO Guide 73:2009, 3.5.1*]*

3.9.5
risk management
coordinated activities to direct and control an ***organization*** *(3.3.1) with regard to risk*

[SOURCE: ISO Guide 73:2009, 2.1]

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.

4.1.1 *Risk management*

The organization shall ensure that risk management is included in processes associated with the design/development, manufacturing and delivery of primary packaging materials with regard to the primary packaging material quality; records shall be maintained (see 4.2.4).

Risk management should be applied but not limited to aspects such as, in alphabetical order, the following:

— *change control,*

— *cleaning,*

— *complaints,*

— *contamination,*

— *design control (new products/new processes),*

— *health and hygiene,*

— *labelling,*

— *maintenance,*

— *materials management,*

— *nonconformities, quality defects,*

— *pest control,*

— *purchasing and supply chain,*

— *rework,*

— *traceability,*

— *validation, verification and qualification.*

NOTE Principles and guidelines on risk management can be found e.g. in ISO 31000, ISO 14971 *or ICH Q9 [35] GAMP5 [33]. For guidance on the various methods for the identification, assessment of risk and severity and control of hazards associated with particular processes or practices, see* IEC 31010.

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 risk management, validation and change control shall be documented.

4.2.1.1 *Administration of computerized systems and data*

There shall be a documented procedure

a) *for the assignment of responsibility to ensure that information technology and the data itself is secure and maintained,*

b) *to ensure that network and files are secure and that only authorized personnel have access to systems and files,*

c) *to ensure file integrity, when files are stored in a shared area, such as a file server, accessed by several workstations,*

d) *covering password management and security routines including 'sleep mode', which shall exist to cover periods of personnel absence from the computer, and*

e) *for the back-up and recovery of electronic product related data, which defines the frequency of back-up, the method and media to be used, and the physical process for safe storage of the data files; the back-up media shall be identified and traceable.*

The organization shall have a documented information technology (IT) recovery plan which details the system for partial and total recovery of data in the event of a failure of the IT system. At defined intervals the system shall be verified to ensure the data can be restored.

If IT systems are changed, access to legacy systems and data shall be defined as part of change control (see 7.5.1.3).

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 shall 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. Records shall clearly demonstrate the identified check and stages. If either check is carried out electronically, this shall be clearly defined.*

4.2.4.4 *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.*

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

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

4.2.4.7 *All manufacturing, control, testing, distribution and investigation records shall be retained for at least five years after the date of manufacture of the primary packaging material or as agreed 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).

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

5.2.1 *Customer audits*

The organization shall approve access by mutual agreement for existing/prospective customers or their nominated representatives to conduct audits to review and to assess the organization's quality management system.

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.

d) *training 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 the following:*

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

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

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.*

6.2.2.1.7 *Contractors and visitors shall receive appropriate instructions prior to entering the manufacturing /production facilities.*

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 system).

6.3.1 *The infrastructure shall be managed, operated and maintained to avoid product contamination, including but not limited to the following:*

— *facilities shall be protected against entry of unauthorized personnel;*

— *personnel entering defined areas in production, storage or quality control/quality assurance shall only access these areas wearing appropriate clothing;*

— *layout, design and operation shall minimize the risk of errors and permit effective cleaning and maintenance to avoid cross-contamination and any adverse effect on the quality of products, based on a risk assessment;*

— *changing, toilet and hand-washing facilities shall be provided for areas where products are processed and handled; where product quality is affected, these facilities shall be separated from manufacturing areas and not ventilated directly to the manufacturing area.*

6.3.2 *Storage areas shall be*

— *of adequate capacity to allow orderly storage of starting materials and products and*

— *appropriate with regard to material and product quality.*

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 *Work 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.*

6.4.1.4 *Where primary packaging materials are exposed, covers shall be used unless justified otherwise through a documented risk assessment.*

6.4.2 *Classification of clean zones/cleanrooms*

Clean zones/cleanrooms shall be classified and monitored/operated.

See ISO 14644-1, ISO 14644-2, ISO 14644-3, ISO 14644-5.

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

If appropriate, biocontamination monitoring shall 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 can 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;*

f) *protective clothing appropriate to the classification of the process area*.

NOTE Automatic door closers, protective air curtains or plastic curtains can be used, to reduce the risk of contamination.

6.4.4 *Pest control*

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

6.4.5 *Materials and 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 can 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*.

6.4.5.4 *Processing aids shall be defined and be subject to a documented risk assessment for their potential impact on the quality of the primary packaging materials and used in a controlled manner*.

6.5 *Maintenance and cleaning 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 can affect product quality*.

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

6.5.3 *Repair and maintenance operations shall not present any hazard to the quality of products. Maintenance operations shall not introduce contamination and, on completion, shall include a documented cleanliness check*.

6.5.4 *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)*.

6.5.5 *The organization shall define and document a cleaning schedule that takes into account the contamination risk*.

NOTE Documented procedures and schedules for cleaning can contain, where applicable, the following:

— *cleaning methods;*

— *materials used, e.g. detergents/disinfectants*;

— *areas/equipment to be cleaned;*

— *precautions and cleaning routines for spillage;*

— *records required.*

Following cleaning, it is good practice to store the equipment in a clean and dry condition and separately from soiled equipment.

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

6.5.7 *Defective quality critical equipment shall be removed from service and/or clearly labelled and product produced evaluated (see 8.2.4). Prior to reintroduction it shall be verified as suitable for use*.

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).

7.2.3.3 *If specified by the customer, samples and certification documents provided for evaluation, stability testing or clinical trials for marketing authorization applications, shall be compliant with the appropriate GMP procedures and controls.*

As part of a marketing authorization application, the customer can require the organization to provide specified information. An appropriately qualified individual within the organization shall approve such information.

EXAMPLE Such information are composition, test data, specifications, control methods and processing conditions.

Changes that affect any of the data supplied by the organization should be communicated to the customer or the regulatory authority, as appropriate (see 7.2.3 and 7.5.1.3).

NOTE To facilitate organization confidentiality, scientific and technical information can be supplied as a dossier directly to the global authorities, for example in the form of a Drug Master File (DMF), or European Pharmacopoeia Certificate of Suitability, in connection with the application for a marketing authorization and records maintained.

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.

NOTE The organization and customer are encouraged to work together to verify the appropriateness of the primary packaging materials for their intended use.

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 *For quality critical materials, the organization shall periodically verify the relevant and/or critical information received from their suppliers on a certificate of analysis (CoA), certificate of conformity (CoC), or certificate of testing (CoT).*

NOTE 1 This can mean performing similar testing on site, by an independent contractor, or routine audit of the facilities to ensure that there is a high level of confidence in the supplier information. Alternatively, an audit can be replaced by a certified management system if justified.

NOTE 2 In lieu of such testing by the organization, a report of analysis, e.g. CoA, CoC or CoT, can be accepted from the supplier, provided that at least one specific identity test is conducted on the material or sub-component by the organization.

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

7.4.3.4 *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 can 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 *Handling/transfer containers shall be clean and not contribute to particulate contamination. For product contact packaging materials they shall be covered or appropriately sealed.*

7.5.1.1.8 *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).*

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

7.5.1.1.10 *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.*

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

7.5.1.1.12 *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).*

NOTE As an example, reusable handling/transfer containers used to hold starting materials during processing are subject to a documented cleanliness check before being loaded with a different material to avoid cross-contamination.

7.5.1.1.13 *Partially, reduced line-clearances or automated changeover systems that are designed to reduce make-ready time and do not permit a total line-clearance, shall be subject to a documented risk assessment and operated with controls to ensure product quality.*

7.5.1.1.14 *Pallets shall be constructed of materials appropriate to the product being handled, sourced and controlled to reduce the risk of contamination.*

NOTE Wooden pallets could be contaminated through migration of any chemicals used in other pallet treatments.

7.5.1.2 *Segregation controls*

In order to reduce the risk of cross-contamination/mix-up of materials, intermediates and finished products, they shall be segregated by suitable means based on a risk assessment e.g. physical segregation, labelling, barcoding, electronic locations.

7.5.1.3 *Change control*

7.5.1.3.1 *The organization shall establish and operate a documented procedure for an effective change control system, incorporating the evaluation of risk(s) associated with all proposed changes that can have potential impact on the quality of supplied product.*

7.5.1.3.2 *The evaluation of the change on the quality of the product shall determine if validation or revalidation is required.*

7.5.1.3.3 *The organization's change control procedure shall ensure supporting data are generated to demonstrate that the change will result in a product of desired quality and safety, consistent with the approved specifications.*

7.5.1.3.4 *Defined functions shall have the responsibility and authority for approval of changes. Approved changes shall be implemented in a controlled manner.*

7.5.1.4 *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 *Equipment, utilities and facilities used for manufacturing primary packaging materials shall be verified 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 can 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 References [27], [32] and [33].

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 and revalidated periodically. 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 code system readers) to verify the continued functionality*.

7.6.2 *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 *Batch release*

The organization shall implement an approval process for the batch release of products from the organization.

NOTE 1 Shipment prior to batch release can occur in accordance with a customer agreement.

If final inspection is a requirement, it shall be completed prior to batch release. Sampling procedures shall be defined to ensure that samples are representative of the batch being assessed. Samples shall not be returned to the production area if removed to a separate testing location.

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

NOTE 2 Final inspection might not include all specification parameters on basis of the control system and control strategy.

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 *Production and control data*

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

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 Artwork/origination and print impression media

A.1.1 General

A.1.1.1 *Artwork/origination files shall be named and stored according to a documented procedure that enables them to be readily identified, issue controlled and traceable.*

A.1.1.2 *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/cylinders

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

A.1.3 Copy/design change

Where a design requires several plates/cylinders 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)/cylinder(s) and the retention of the other media within the set. The original plates/cylinders 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 recognized and classified as an acute contributory risk relating to admixtures. Therefore this shall only be permitted in agreement with the customer and on completion of a documented risk assessment to evaluate and mitigate the risk of cross-contamination, (see 7.2.3).

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.2.7.6 *For reel-fed production on continuous basis there shall be a suitable method to ensure product separation; the subsequent processes shall be verified to ensure correct separation of products and removal of defined gap material.*

EXAMPLE Defined change-over or gap between each printed job e.g. printed dummy text or blank material, code reading and code verification.

A.3 Security code systems

A.3.1 General

To ensure the security of the product and prevent cross-contamination, security code systems 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.

NOTE Common security code systems are e.g. barcode system, data matrix code, tag technology.

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 code system, each colour of the design should be included in the code. For all code systems, 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 coded item shall be verified by online scanning equipment to ensure that the codes are readable and that the correct product is being produced. Scanning of security codes should be carried out during the last feasible production process.*

A.3.2.2 *The scanning equipment software/control configuration shall be controlled to prevent unauthorized tampering. Where feasible, codes shall be loaded from an independent source, e.g. specification or approved proof.*

A.3.2.3 *There shall be an effective system for rejecting any product that fails the scanning process. Any product rejected by the online 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 online 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 coded 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 security code 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 codes from all lanes shall be carried out.*

A.3.3 "Point of sale" codes

Where "point of sale" codes (GS 1/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, qualification and validation requirements for primary packaging materials

B.1 General

This informative annex describes the approach when verification or qualification and validation is required.

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

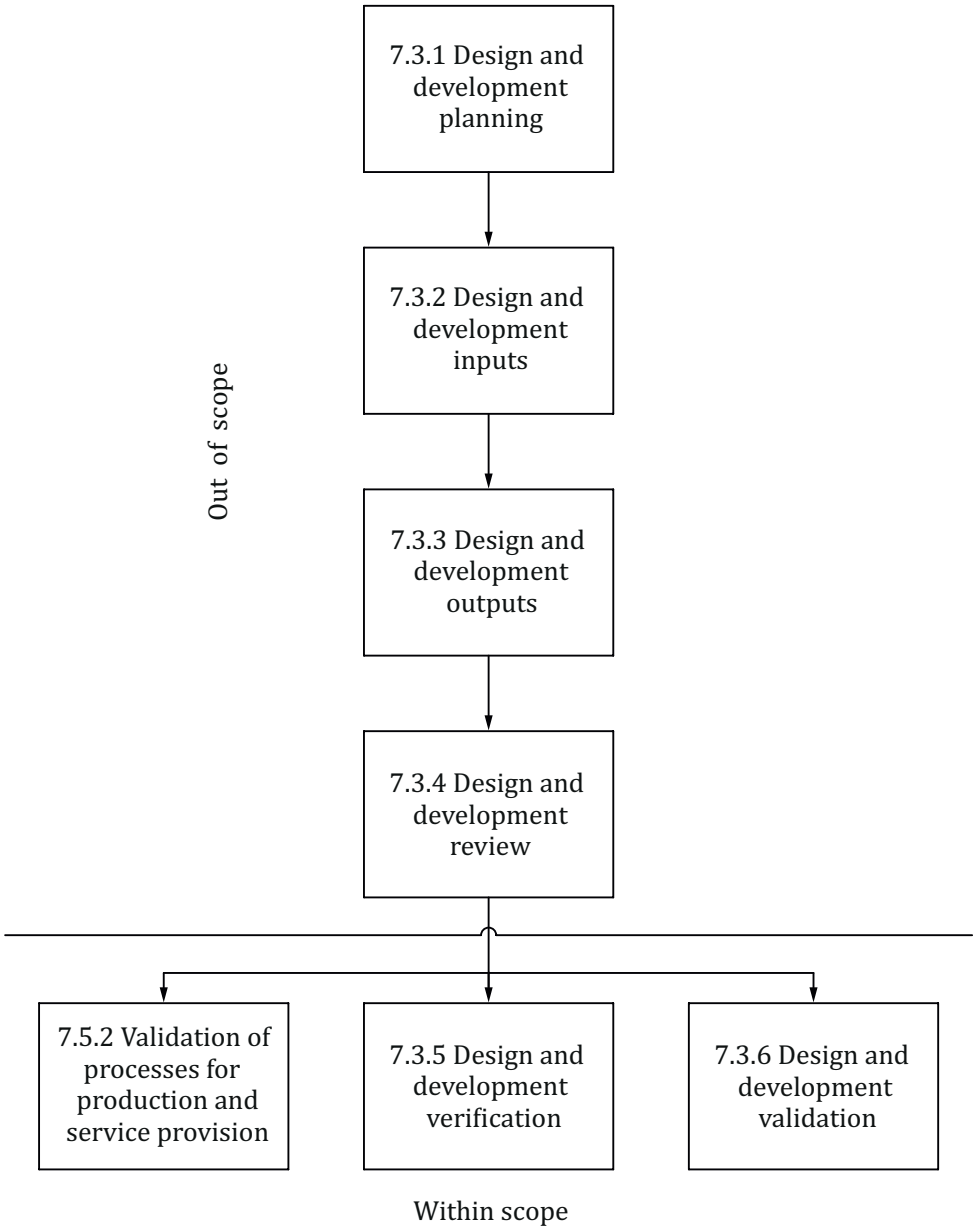


Figure B.1 — Scope of this annex

Throughout this annex only equipment verification/qualification and process/product validation will be mentioned.

When design and development is related to equipment, design and development verification is equal to equipment verification/qualification.

When design and development is related to processes or products, design and development validation is equal to process/product validation.

Items which can require verification/qualification include the following:

— *equipment used for production of primary packaging materials, utilities and facilities;*

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

Items which can require validation include the following:

— *validation of processes;*

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

The aim of verification/qualification/validation is to confirm through documented evidence that pre-determined specification are consistently fulfilled.

B.2 Guidance considerations

B.2.1 General

A documented risk assessment is used to determine which equipment and processes need to be verified/qualified/validated. Product validation is optional, either after an internal decision of the organization or at the request of the customer.

Verification/qualification of equipment and validation of processes/product can be performed independent from each other, e.g. validation of a new process/product does not require re-verification/re-qualification of existing equipment.

B.2.2 Considerations prior to verification/qualification/validation

Prerequisites to verification/qualification of the equipment are the following:

— *approved/agreed upon requirement specifications;*

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

— *definition of critical process parameters;*

— *training like GMP and verification/qualification.*

Prerequisites to validation of the process/product are the following:

— *approved/agreed upon process/product specification;*

— *verified/qualified equipment;*

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

— *definition of critical process parameters;*

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

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

B.2.3 Software validation

Software can be validated/verified (see 7.5.2.7 and 7.5.2.8) by functional tests. Software which is part of the equipment can be included in the equipment verification/qualification.

NOTE The GAMP guideline[33] might give guidance how the functional test can be executed.

B.3 Validation master plan (VMP)

B.3.1 General

The validation master plan (VMP) describes the validation (includes in this case also verification/qualification) activities and the order of execution in accordance with the overall validation approach. It is recommended to revise the plan on a regular basis, for example yearly.

It should usually include the following elements:

— *validation planning (see B.3.2) and scheduling;*

— *organizational structure of validation activities — roles and responsibilities (see B.3.3);*

— *summary of quality critical equipment, process (see B.3.4 and B.3.5) and product (only in case of customer related validations);*

— *references to existing documents (e.g. reference to an existing validation report), if applicable;*

— *references to applicable procedures (e.g. overall validation approach, documentation format).*

In case of large projects (different verifications/qualifications/validations are combined in one project), it can be advisable to create separate validation master plans.

B.3.2 Validation planning

B.3.2.1 General

Prospective validation is recommended as preferred approach but under certain circumstances a concurrent or retrospective validation can be accepted (this statement is not valid for sterilization processes, see 7.5.2.11).

B.3.2.2 Prospective validation

Prospective validation occurs prior to commercial production.

B.3.2.3 Concurrent validation

Concurrent validation should only apply to performance qualification and process validation.

Concurrent validation consists of activities conducted in parallel with the manufacture of commercial product where the commercial product is released before the conclusion of validation activities. Concurrent validation should follow the principles and procedures associated with prospective validation.

Validation that takes place in campaigns represents a speciality in the manufacture of primary packaging material. In several cases, machines/lines are used for campaign production. In these cases, concurrent validations may be interrupted (also for longer periods of time) and resumed with the next production campaign.

B.3.2.4 Retrospective validation

Retrospective validation implies that commercial product has been released prior to the conclusion of validation activities.

This approach includes establishing documented evidence that installed and operating equipment produces a consistent product by performing a historic review of data generated over the range of operating parameters and raw materials. This review can include maintenance and engineering records, quality records and customer complaints.

B.3.2.5 Bracketing/matrix approach

In general, a bracketing/matrix approach can be appropriate based on risk analysis.

Where the equivalence of equipment has been proven, a bracketing/matrix approach can be used to

— *reduce number of installation and operational testing during equipment verification/qualification,*

— *reduce number of PQ (performance qualification) batches during equipment qualification,*

— *reduce number of PV (process validation) batches during product or process validation, and*

— *increase the re-validation period for individual equipment and performing the re-validation on equivalent equipment alternately.*

The following overview demonstrates how this can be used.

Table B.1 — Example on use of matrix approach

type of validation	machine 1 (equivalent with 2 and 3)	machine 2 (equivalent with 1 and 3)	machine 3 (equivalent with 1 and 2)
initial validation	3 batches	1 batch	1 batch
re-validation: 1st year	1 batch	not done	not done
re-validation: 2nd year	not done	1 batch	not done
re-validation: 3rd year	not done	not done	1 batch
re-validation: 4th year	1 batch	not done	not done

Where a range of products are produced in accordance with a same process, an experimental design to test only the extremes of, for example, smallest and largest product may be used to reduce the number of validation batches. The design assumes the extremes will be representative of all the samples between the extremes. In case a worst case can be defined, it is sufficient to test the worst case only instead of the extremes.

In all cases, there should be sufficient process and product knowledge on which to base a sound rationale.

The equivalence of equipment, the technical rationale and justification for decision have to be documented.

B.3.3 Roles and responsibilities

Detailed information concerning roles and responsibilities (naming the individuals with responsibility for conducting the validation steps and authorizing the results) should be part of the respective validation documents and should be specified prior to the commencement of work unless it is defined in other documents or procedures.

B.3.4 Quality critical equipment

Risk assessment is an inherent part of the decision-making process and can be used to determine whether verification or qualification of equipment is required, therefore all equipment should be assessed for their potential impact on the quality of the product.

Equipment is critical in case one of the following questions is answered with yes.

— *Would malfunction of the equipment impact directly on product quality as defined for the type of products it is producing?*

— *Is the equipment used to guarantee sterility of the products?*

— *Does the equipment control or measure quality critical processing steps or parameters?*

— *Does the equipment produce data/records for acceptance or rejection?*

— *Is equipment in direct contact with the product?*

— *Is the equipment used to prevent contamination, to remove contamination or to clean?*

When equipment is considered critical, verification or qualification should be performed and it is included in the validation master plan.

When equipment is not critical, good engineering practices apply and it is not included in the validation master plan.

B.3.5 Quality critical processes

Process validation is performed where the resulting output cannot be verified by subsequent monitoring or measurement. This includes processes where deficiencies become apparent only after the product is in use (see 7.5.2.1).

The following decision model can be used to determine whether the process is critical or not, based on the risk that products will be released, which are not within the predetermined specifications:

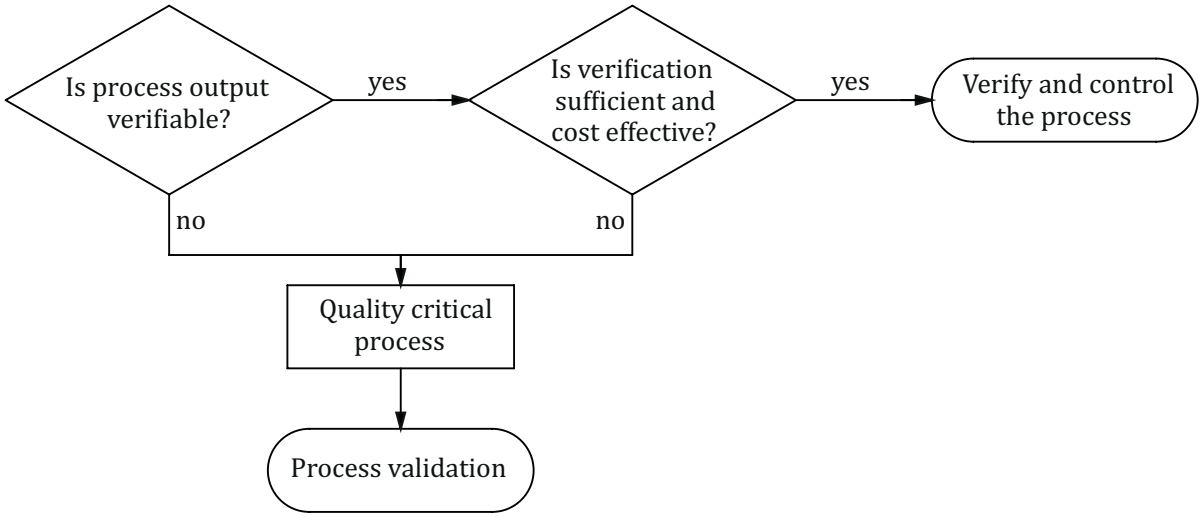


Figure B.2 — Decision tree for process validation/quality critical process

B.4 Verification/qualification/validation implementation

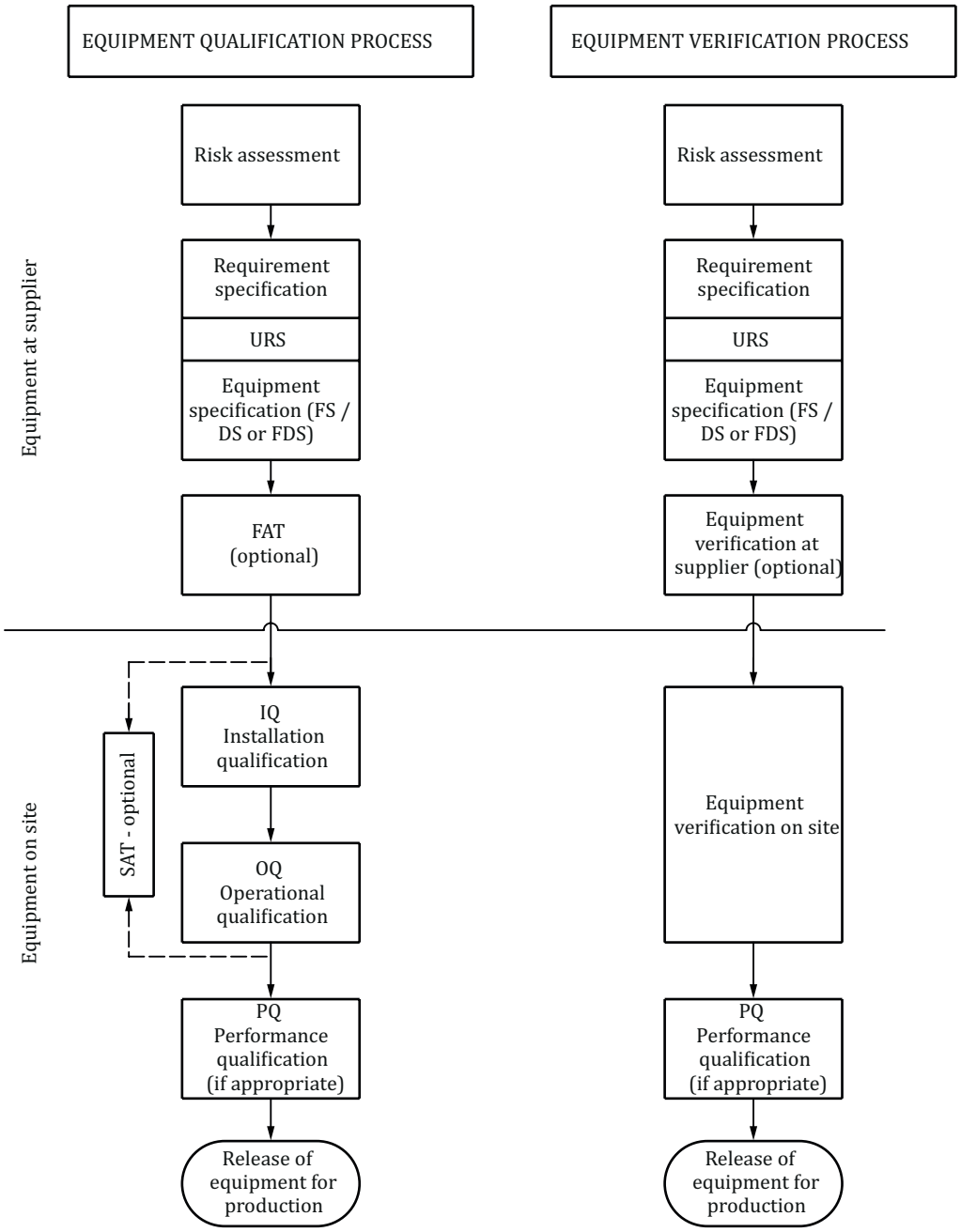
B.4.1 Verification or qualification stages

B.4.1.1 General

The verification or qualification should be based on a risk assessment.

Equipment verification/qualification consists of the following stages: risk assessment, requirement specification setting and verification/qualification.

A decision on the type of documentation required should be taken at the start of the process and documented unless it is defined in validation procedures.



Key

DS design specification
FAT factory acceptance test
FDS functional design specification
FS functional specification
SAT site acceptance test
URS user requirement specification

Figure B.3 — Verification/qualification stages

B.4.1.2 Risk assessment

Risk assessment should underpin the specification and verification/qualification process, and be appropriately applied at each stage and documentation should be based on the risk to product quality.

B.4.1.3 Requirement specification

B.4.1.3.1 General

The requirement specifications can be combined in one or more specification documents depending on the criticality of the equipment whether it concerns standardized or customized equipment or depending on the responsibilities (organization or supplier). Every specification should contain well defined, specific, testable, achievable acceptance criteria.

B.4.1.3.2 User requirement specification

A URS as defined in 3.7.4 is an approved document that states the product specifications of the material produced on this equipment as well as functional, operational and/or technical aspects of the equipment or process required to produce the desired product. The URS can include the consideration for equipment lay-out with sufficient space for material flow and operators, availability of spare parts, and ease of access for cleaning and line clearance. Alternatively, this information can be provided in other documentation.

B.4.1.3.3 Equipment specification

It is important that all critical aspects are included in the specifications.

Critical aspects of manufacturing systems are typically functions, features, abilities and performance or characteristics necessary for the manufacturing process and system to ensure consistent product quality.

B.4.1.4 Equipment verification/qualification

A systematic approach should be defined to verify that the equipment is fit for intended use, has been properly installed and is operating correctly as defined in the requirement specifications. The extent of verification/qualification and the level of detail of documentation should be based on risk, including those associated with product quality, and the complexity and novelty of the equipment.

Verification/qualification can be split in two sub-stages: installation qualification and operational qualification, but it is also possible to combine the installation and operational testing in one stage like it is typically done during testing at supplier and testing on site.

Leveraging of data are allowed, e.g. data obtained during testing at the supplier do not have to be repeated on site unless the transfer of the equipment influences the testing.

Installation testing should include: verification if equipment is installed as per the specifications, is calibrated, where appropriate.

Operational testing should include: verification of operation of the equipment at upper and lower ends of the required operating limits.

B.4.1.5 Perfomance qualification

PQ testing uses production materials to verify that the equipment is robust and the primary packaging material can be consistently produced under routine operating conditions. PQ challenges the overall line performance to ensure that it can produce consistently at the quality standard required. The test process and results of an appropriate number of consecutive production batches (typically three) are formally documented and approved.

Based on risk management (e.g. standard equipment and all product specifications are tested on every batch before release), performance qualification can be skipped or can also be combined with process or product validation.

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.4.2 Process and product validation

B.4.2.1 Process validation

A process validation consists of a number of consecutive production batches (typically three) produced under normal conditions with a higher level of sampling and additional testing compared to routine production. Process validation can be combined with PQ. In case of lengthy production processes, the same exception is valid for PV batches (see B.4.1.5).

Process validation has to be based on a firm base of knowledge of the process and its variables/variations.

Process validation is independent of the product. Bracketing or matrix approach may be used.

B.4.2.2 Product validation

The approach is in line with process validation; however, specific customer requirements can be added.

B.5 Documentation for the verification, qualification and validation

B.5.1 General

All documents should be reviewed and approved prior to the commencement of verification/qualification/validation/release.

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

Any revision of a document should be tracked by version control.

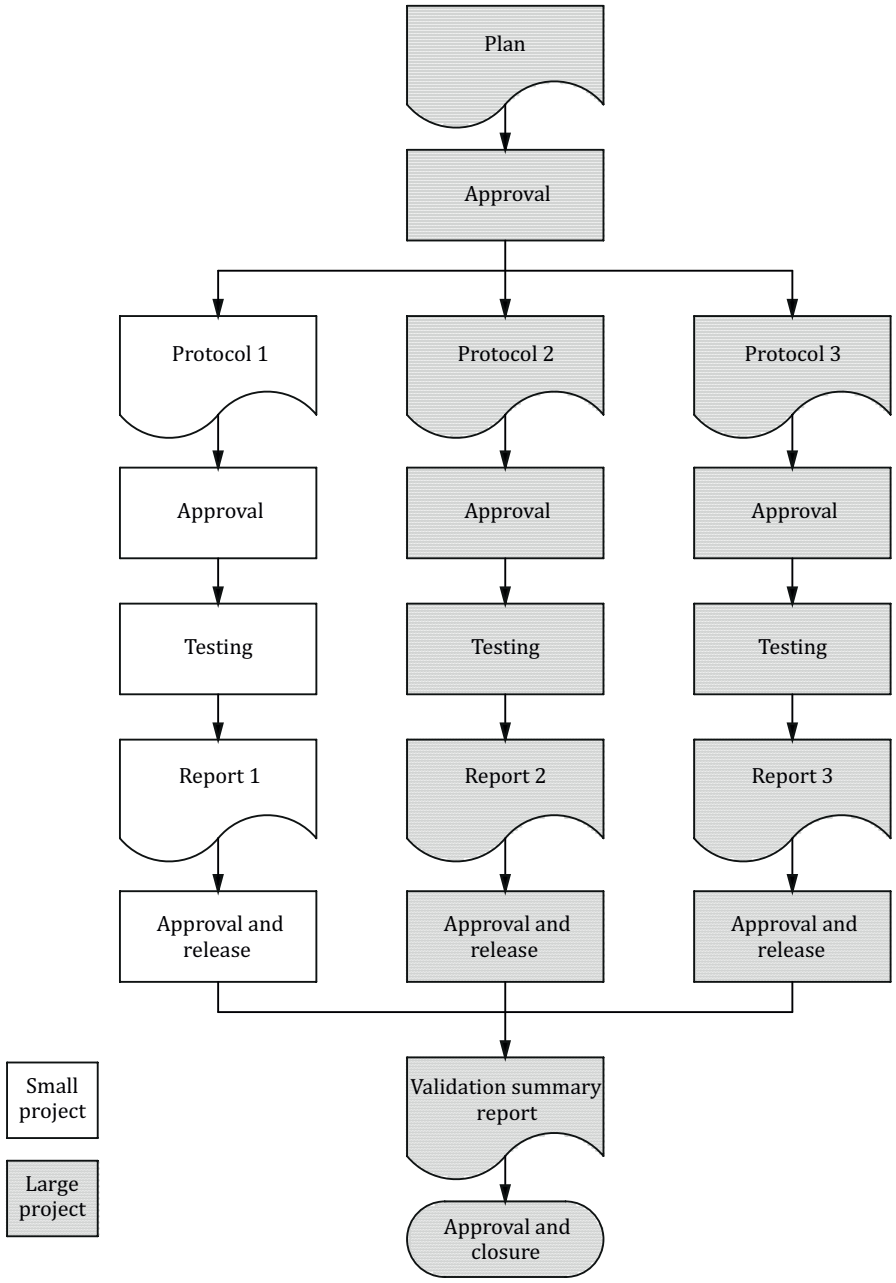


Figure B.4 — Example of documentation structure

B.5.2 Plan (optional)

One or more plans can be created to detail the steps to be taken in the different stages of the verification/qualification/validation of a project unless detailed in validation procedures.

These plans can include the following:

— *description of the project/scope;*

— *roles and responsibilities;*

— *planning;*

— *risk analysis;*

— *overall acceptance criteria;*

— *validation approach;*

— *documents to be created;*

— *reference to procedures and change control;*

— *definition of conditions for quarantine status of batches subject to PQ or validation.*

Plan and protocol may be combined in one document.

B.5.3 Protocol

A written protocol should be established that specifies how verification/qualification/validation will be conducted.

The protocol can include the following:

— *description of the project/scope;*

— *roles and responsibilities;*

— *justification of the approach taken;*

— *tests to be performed with test methods and test conditions;*

— *detailed acceptance criteria for each test;*

— *sampling plan;*

— *critical process parameters;*

— *reference to procedures, change control and requirement specifications;*

— *prerequisites.*

B.5.4 Report

A report that cross-references the verification/qualification/validation protocol should be prepared.

The report can include the following:

— *summary of test results;*

— *raw data;*

— *deviations observed and corrective actions taken or to be taken;*

— *conclusion;*

— *changes to the plan as defined in the protocol with appropriate justification.*

After completion of a satisfactory testing, a formal release for the next step in verification/qualification/validation should be made as a written authorization.

B.5.5 Validation summary report — VSR (optional)

The validation summary report follows completion of all stages of verification/qualification/validation, which concludes the project.

The validation summary report can include the following:

— *cross-reference to protocols and reports;*

— *changes to plans and justification for any change;*

— *formal approval and closure of the project.*

B.5.6 Archiving

Verification or qualification and validation records should be maintained according to 4.2.4.8.

B.6 Validation maintenance

B.6.1 General

The verification/qualification of equipment and validation of process(es)/product should be maintained. Any changes should be risk assessed for their impact on the validation status. If necessary, appropriate verification/qualification/validation or re-qualification/re-validation should be performed.

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

B.6.2 Change control

Specific controls should be implemented to cover changes during verification/qualification/validation. Formal, documented change control should be implemented after release of the equipment/process/product and kept throughout the lifetime of the equipment/process/product.

B.6.3 Follow-up

Action should be taken to complete any outstanding actions, e.g. deficiencies following verification/qualification/validation.

All actions taken should be documented.

B.6.4 Preventive maintenance

After release of equipment a preventive maintenance plan (including calibration) should be established to guarantee equipment performance.

B.6.5 Re-qualification/re-validation

As long as the equipment/process operates in a state of control and no changes have been made to the equipment/process or output product, the equipment need not be re-qualified and process need not be re-validated. Whether the equipment/process is operating in a state of control is determined by analysing day-to-day process control data and any product testing data for conformance with specifications and for variability.

When changes or deviations occur, the equipment/process should be reviewed and evaluated, and re-qualification/re-validation should be performed where appropriate.

Periodic qualifications/validations can be required e.g. clean rooms, sterilization processes.

Annex C
(informative)

Relationship between clauses of this International Standard and the high level structure

This Annex describes the relationship between the clauses/subclauses of this International Standard and the clauses/subclauses as given in the high level structure for use in management systems standards according to the ISO/IEC Directives Part 1, Annex SL, Appendix 2. It is intended to align the structure of ISO 15378 with that of the high level structure as given in the ISO/IEC Directives Part 1, once the revision of ISO 9001, being the basis of this International Standard, has been completed.

Table C.1 — Relationship between this International Standard and the high level structure for use in management system standards (see ISO/IEC Directives Part 1, Annex SL, Appendix 2) (1 of 4)

Clause(s)/subclause(s) of this International Standard	Clause(s)/subclause(s) of the high level structure for Management System Standards according to the ISO/IEC Directives Part 1, Annex SL, Appendix 2	Remarks
1 (Scope)	1 (Scope)	
2 (Normative references)	2 (Normative references)	
3 (Terms and definitions)	3 (Terms and definitions)	
5.2 (Customer focus) 5.6 (Management review)	4 (Context of the organization) 4.1 (Understanding the organization and its context)	
5.2 (Customer focus)	4 (Context of the organization) 4.2 (Understanding the needs and expectations of interested parties)	
4.2.2 (Quality Manual)	4 (Context of the organization) 4.3 (Determining the scope of the quality management system)	
4.1 (Quality management system)	4 (Context of the organization) 4.4 (Quality management system)	
5 (Management responsibility) 5.1 (Management commitment) 5.2 (Customer focus)	5 (Leadership) 5.1 (Leadership and commitment)	
5.3 (Quality policy)	5 (Leadership) 5.2 (Policy)	
5.5 (Responsibility, authority and communication)	5 (Leadership) 5.3 (Organizational roles, responsibilities and authorities)	
5.4.2 (Quality management system planning) 4.1.1 (Risk management)	6 Planning) 6.1 (Actions to address risks and opportunities)	

Table C.1 *(continued)*

Clause(s)/subclause(s) of this International Standard	Clause(s)/subclause(s) of the high level structure for Management System Standards according to the ISO/IEC Directives Part 1, Annex SL, Appendix 2	Remarks
5.4 (Planning) 5.4.1 (Quality objectives) 5.4.2 (Quality management system planning)	6 (Planning) 6.2 (Quality objectives and planning to achieve them)	
6.1 (Provision of resources) 6.3 (Infrastructure) 6.4 (Work environment) 6.5 (Maintenance and cleaning activities)	7 (Support) 7.1 (Resources)	
6.2 (Human resources)	7 (Support) 7.2 (Competence)	
6.2.2 d)	7 (Support) 7.3 (Awareness)	
5.5.1 (Responsibility and authority) 5.5.3 (Internal communication) 7.2.3 (Customer communication)	7 (Support) 7.4 (Communication)	
4.2 (Documentation requirements)	7 (Support) 7.5 (Documented information)	
7 (Product realization) 7.1 (Planning of product realization) 7.2 (Customer-related processes) 7.3 (Design and development) 7.4 (Purchasing) 7.5 (Production and service provision) 7.6 (Control of monitoring and measuring equipment) 8.3 (Control of nonconforming product)	8 (Operation) 8.1 (Operational planning and control)	
8.1 (General) 8.2 (Monitoring and measurement) 8.2.3 (Monitoring and measurement of processes) 8.2.4 (Monitoring and measurement of product) 8.4 (Analysis of data)	9 (Performance evaluation) 9.1 (Monitoring, measurement, analysis and evaluation)	
8.2.2 (Internal audit)	9 (Performance evaluation) 9.2 (Internal audit)	

Table C.1 *(continued)*

Clause(s)/subclause(s) of this International Standard	**Clause(s)/subclause(s) of the high level structure for Management System Standards according to the ISO/IEC Directives Part 1, Annex SL, Appendix 2**	**Remarks**
5.6 (Management review)	9 (Performance evaluation) 9.3 (Management review)	
8.5 (Improvement) 8.3 (Control of nonconforming product) 8.5.2 (Corrective action) 8.5.3 (Preventive action)	10 (Improvement) 10.1 (Nonconformity and corrective action)	
8.5 (Improvement 8.5.1 (Continual improvement)	10 (Improvement) 10.2 (Continual improvement)	

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