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Needle-based injection systems for medical use — Requirements and test methods —

Part 3: Containers and integrated fluid paths

Systèmes d'injection à aiguille pour usage médical — Exigences et méthodes d'essai —

Partie 3: Conteneurs et chemins de fluide intégrés

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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 of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 84, *Devices for administration of medicinal products and catheters*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 205, *Non-active medical devices,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This third edition cancels and replaces the second edition (ISO 11608-3:2012), which has been technically revised.

The main changes are as follows:

— test methods and dimensions specific to traditional pen-injector “Type A” cartridges have been removed.

A list of all parts in the ISO 11608 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user’s national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

Developers and manufacturers of NIS are encouraged to investigate and determine if there are any other requirements relevant to the safety of their products.

Previous editions of this document focused on multi-dose pen-injector cartridges, important dimensions (e.g. inner diameter) and related attributes (e.g., disc seal eccentricity, meniscus) deemed critical for pen-injector form, fit, and function. The previous edition (i.e. ISO 11608-3:2012) included a more general discussion of "other containers" like syringes given their role in single dose NIS with automated functions (commonly referred to as auto-injectors).

Needle-based injection systems for medical use — Requirements and test methods —

Part 3: Containers and integrated fluid paths

1 Scope

This document specifies requirements and test methods for design verification of containers and integrated fluid paths used with Needle-Based Injection Systems (NISs) according to ISO 11608-1.

It is applicable to single and multi-dose containers either filled by the manufacturer (primary container closure) or by the end-user (reservoir) (e.g. cartridges, syringes) and fluid paths that are integrated with the NIS at the point of manufacture.

This document is also applicable to prefilled syringes (see ISO 11040-8) when used with a NIS (see also scope of ISO 11608-1:2022).

This document is not applicable to the following products:

— sterile hypodermic needles;

— sterile hypodermic syringes;

— sterile single-use syringes, with or without needle, for insulin;

— containers that can be refilled multiple times;

— containers intended for dental use;

— catheters or infusion sets that are attached or assembled separately by the user.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements 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 7864:2016, *Sterile hypodermic needles for single use — Requirements and test methods*

ISO 8872, *Aluminium caps for transfusion, infusion and injection bottles — General requirements and test methods*

ISO 9626:2016, *Stainless steel needle tubing for the manufacture of medical devices — Requirements and test methods*

ISO 10555-1:2013, *Intravascular catheters — Sterile and single-use catheters — Part 1: General requirements*

ISO 10555-5:2013, *Intravascular catheters — Sterile and single-use catheters — Part 5: Over-needle peripheral catheters*

ISO 10993-11, *Biological evaluation of medical devices — Part 11: Tests for systemic toxicity*

ISO 10993-17, *Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances*

ISO 11040-4, *Prefilled syringes — Part 4: Glass barrels for injectables and sterilized subassembled syringes ready for filling*

ISO 11040-5, *Prefilled syringes — Part 5: Plunger stoppers for injectables*

ISO 11040-6, *Prefilled syringes — Part 6: Plastic barrels for injectables and sterilized subassembled syringes ready for filling*

ISO 11040-8, *Prefilled syringes — Part 8: Requirements and test methods for finished prefilled syringes*

ISO 11607-1, *Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems*

ISO 11608-1:2022, *Needle-based injection systems for medical use — Requirements and test methods — Part 1: Needle-based injection systems*

ISO 13926-1, *Pen systems — Part 1: Glass cylinders for pen-injectors for medical use*

ISO 13926-2, *Pen systems — Part 2: Plunger stoppers for pen-injectors for medical use*

ISO 13926-3, *Pen systems — Part 3: Seals for pen-injectors for medical use*

ISO 21881, *Sterile packaged ready for filling glass cartridges*

ISO 80369-7, *Small-bore connectors for liquids and gases in healthcare applications — Part 7: Connectors for intravascular or hypodermic applications*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 11608-1 and the following apply.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
cartridge
container for the medicinal product that is closed on one end with a *cartridge cap* (3.2) and *disc* (3.5), and on the other end with a *plunger stopper* (3.8)

3.2
cartridge cap
component that attaches the *disc* (3.5) to the *cartridge* (3.1)

3.3
container closure integrity
CCI
adequacy of primary container closure to maintain a *sterile barrier* (3.10) against potential contaminants until the labelled expiration date or first intentional user interaction

3.4
fragmentation
formation of elastomeric particles that are generated when the *disc* (3.5) or other elastomeric components that forms part of the primary container closure is pierced by a needle, spike or other access device for filling or delivery

Note 1 to entry: Disc coring is one mechanism to generate fragments.

3.5
disc
septum
elastomeric closure
component of a container [typically a *cartridge* (3.1)], which seals the end of the container through which the medicinal product is accessed

3.6
integrated fluid path
needle-based injection system pathway (NIS), integrated into the NIS at the time of manufacture, that the medicinal product follows from the container or reservoir to the targeted delivery site

3.7
medicinal product compatibility
evaluation of the medicinal product quality based on combined use with the needle-based injection system

Note 1 to entry: Impact of medicinal product on device is covered in ISO 11608-1.

3.8
plunger stopper
component that seals one end of the container and moves within the container to cause or accommodate movement of the medicinal product

3.9
sterility assurance level
SAL
probability of a single viable microorganism occurring after sterilization

Note 1 to entry: It is expressed as the negative exponent to the base 10.

[SOURCE: ISO 11139:2018, 3.275 — modified, "on an item" has been deleted.]

3.10
sterile barrier
system of components that provide a barrier to microbial ingress

4 Requirements

4.1 General

These requirements apply to containers or integrated fluid paths intended to be used with a NIS. When test methods and specifications are noted, they are included to assist manufacturers and suppliers in supporting conformity with design specification of the NIS.

Annex F provides illustrated examples of Primary Container Closures (PCC), reservoirs and fluid path configurations for manufacturer filled and user filled NIS.

Specific requirements for NIS primary container closure system components are:

a) glass syringes (including integrated needles) shall conform with applicable requirements of ISO 11040-4 and ISO 11040-8;

b) plastic syringes (including integrated needles) shall conform with applicable requirements of ISO 11040-6 and ISO 11040-8;

c) prefilled syringes (including integrated needles) shall conform with applicable requirements of ISO 11040-8;

d) syringe plunger stoppers shall conform with applicable requirements of ISO 11040-5;

e) glass cartridges shall conform with applicable requirements of ISO 13926-1 and ISO 21881;

f) cartridge plunger stoppers shall conform with applicable requirements of ISO 13926-2;

g) cartridge discs shall conform with applicable requirements of ISO 13926-3;

h) cartridge caps shall conform with applicable requirements of ISO 8872;

i) all reservoirs provided empty to the user shall be free of droplets of fluid (lubrication) on the outside or inside surfaces when inspected in accordance with ISO 11608-1:2022, 11.3.

4.2 Container integrity

4.2.1 Container Closure Integrity (CCI)

Container closure integrity shall be ensured until the expiration date or the first intentional user interaction that breaks CCI.

If the NIS is manufacturer-assembled with a primary container closure to form a single integral unit, the manufacturing processes, including assembly, shall be shown to not adversely impact container closure integrity, in accordance with applicable pharmacopeia.

4.2.2 Resealability — All multi-dose cartridges or reservoirs with discs

For all cartridges or reservoirs with discs intended for multiple penetrations, after having been penetrated in accordance with the test method specified in 5.1, the penetrated discs of 20 cartridges or reservoirs shall not leak from the penetration site when the cartridge is pressurized.

The disc of the cartridge or reservoir shall be punctured a minimum of 1,0 times the maximum number of penetrations expected during its intended use. Risk assessment shall assess the impact of resealability on the function of the NIS to determine if a greater safety factor is required.

4.2.3 Fragmentation (disc coring) – cartridges or reservoirs with discs

Cartridges or reservoirs that are accessed through an elastomeric disc with a needle, spike or other access device for delivery shall not exceed six elastomeric disc fragments in the visible range (>150 µm in diameter) per 100 punctures in accordance with the method described in 5.2, collected from both coring (ejected from the needle) and fragmentation (collected from the liquid expelled from the container or reservoir).

For single-dose cartridges, a single penetration on each cartridge or reservoir shall be performed.

For multi-dose cartridges or reservoirs, each disc (barrier) shall be punctured a minimum of 1,0 times the maximum number of penetrations expected during its intended use.

Risk assessment shall assess the impact of fragments on the function of the NIS to determine if a greater safety factor, additional mitigations or lowering the limit of allowed fragments shall be required.

NOTE The impact of any fragments on the function of the NIS can be assessed through dose accuracy testing.

4.3 Cannula requirements (as part of the fluid path)

4.3.1 Rigid needles

If the integrated fluid path contains a rigid needle, the strength of union between the needle at its connection point to the NIS shall not break when subjected to the minimum force given in ISO 7864:2016, Table 2 when tested according to ISO 7864:2016, Annex B. The directions of force shall be applied as the needle would encounter during removal from the injection site.

For tapered needles, the minimum force given in ISO 7864:2016, Table 2 shall be determined by the outer diameter at the hub as indicated in ISO 7864:2016, Figure 1.

The performance of the rigid needle part shall fulfil the requirements in ISO 9626:2016, Clause 5 and ISO 7864:2016, 4.10.4 (paragraph 1), 4.11, 4.12 and 4.13, or an equivalent and applicable standard for tubing suited to medical use but fabricated in materials other than stainless steel, to ensure the rigid needle performs as intended for the specific design.

4.3.2 Soft cannulas

If the integrated fluid path contains a soft cannula and an introducer needle, the strength of union between the soft cannula and NIS, or the introducer needle and the NIS, shall meet the requirements of ISO 10555-5:2013, 4.3.3.4 to ensure the soft cannula and/or introducer needle remains affixed to the NIS throughout its intended use. The testing shall consider and address the forces and vectors that the introducer needle and cannula would encounter during removal from the injection site.

In addition, the soft cannula shall meet the requirements of ISO 10555-1:2013, 4.6 to ensure the soft cannula performs as intended for the specific design. Additional physical and functional evaluations to be considered can include flexural fatigue, compression force, kink resistance, burst testing, etc. Risk assessment shall be relied upon to determine appropriate evaluations.

In addition, Annex A can also be of assistance.

4.4 Fluid line connections

If the NIS requires a separate external fluid line to connect the functional core of the NIS to a distant injection site, any connections along that fluid line shall withstand a static tensile force of not less than 15 N for 15 s.

If any connection uses a Luer connection, the connector shall conform with ISO 80369-7.

4.5 Medicinal product compatibility

4.5.1 General

All materials of the NIS in direct contact with the medicinal product shall be compatible with the medicinal product.

When the NIS is filled by the manufacturer, and the container and/or the integrated fluid path are designed to protect the medicinal product through shipment and storage, it shall be considered part of the primary container closure.

NOTE 1 The requirements for assessing the adequacy of the PCC is covered by applicable pharmacopeia and ICH Guidance and are not addressed within this document.

NOTE 2 Annex A provides a reference to some relevant requirements, guidance, standards or compendia material for each topic below.

4.5.2 Medicinal product compatibility with reservoir and integrated fluid path materials

Reservoir and integrated fluid path materials that can come into contact with the medicinal product shall not adversely affect the quality of the medicinal product for the intended time of contact. These requirements apply to the medicinal product after delivery through the NIS.

NOTE Annex E provides a discussion of medicinal product compatibility.

4.5.3 Reservoir and integrated fluid path particulate matter

4.5.3.1 General

The reservoir and/or integrated fluid path shall be assessed for sub-visible and visible particulate matter.

Applicable pharmacopeia establishes limits for the size and number of particulates allowed for the medicinal product. A portion or subset of the particulate matter limit can be generated by the reservoir and/or fluid path during delivery. Manufacturers shall establish particulate matter limits of the reservoir and/or fluid path based on risk assessment and applicable pharmacopeia.

It is recommended that the manufacturer and its supplier agree upon the test methods to be used and the allocation of size and number of sub-visible and visible particulate matter permissible for the NIS.

Particulates, which, due to their size, nature and/or quantity interfere with the function of the NIS, medicinal product compatibility or have a negative impact to patient safety, shall not be acceptable.

NOTE The impact of any particulates on the function of the NIS can be assessed through dose accuracy testing.

4.5.3.2 Sub-visible

Unless otherwise justified, limits for the NIS reservoir and/or integrated fluid path shall be:

— Particles ≥10 µm: 600 max. per NIS;

— Particles ≥25 µm: 60 max. per NIS;

when tested, for example, in accordance with the method described in 5.3.

NOTE These above listed limits are taken from ISO 11040-4:2015.

4.5.3.3 Visible

Visible particulate matter (>150 µm in diameter) other than fragments generated during disc penetration, which are addressed in 4.2.3, for the NIS reservoir and/or integrated fluid path shall not be present when tested, for example, in accordance with the method described in 5.4.

NOTE The above listed limit is taken from United States Pharmacopeia (USP).

4.5.4 Reservoir and fluid path pyrogenicity

4.5.4.1 General

Reservoirs and fluid path NISs shall be nonpyrogenic. Studies for determination of nonpyrogenicity shall be conducted on the final NIS or reservoir and/or integrated fluid path components of the NIS, or both, that have been exposed to all NIS manufacturing processes, including sterilization if applicable.

4.5.4.2 Endotoxin-mediated pyrogenicity

The NIS reservoir and/or integrated fluid path shall not exceed the lesser of 0,5 EU/ml (Endotoxin Units) or 20 EU per NIS. If more restrictive limits are required, the manufacturer shall define endotoxin-mediated pyrogenicity limits for the NIS reservoir and/or integrated fluid path through risk assessment.

NOTE See Annex A for further information.

4.5.4.3 Material-mediated pyrogenicity

It shall be demonstrated that the NIS reservoir and/or integrated fluid path conforms to ISO 10993-11 for material-mediated pyrogenicity.

4.5.5 Reservoir and integrated fluid path leachables

Studies to quantify leachable (organic and inorganic chemical) entities that migrate from the reservoir and integrated fluid path into the medicinal product shall be performed and assessed against acceptable limits established in accordance with ISO 10993-17. The studies shall be conducted on the final NIS or reservoir and/or integrated fluid path components of the NIS, or both, that have been exposed to all NIS manufacturing processes, including sterilization if applicable.

The design of leachables studies shall consider in-use testing with the medicinal product (under the conditions of use over the duration of contact) and potential for change or degradation of the materials of the NIS over time.

The results of the studies shall be used to determine the suitability of the NIS for that medicinal product, balancing any identified risks with the clinical benefit to the patient associated with its use.

NOTE 1 See Annex D for additional details on leachables.

Leachables studies are required in this document. However, extractables studies should be performed in order to identify the substances which can be extracted from the materials. Chemical characterization of the reservoir and fluid path can be performed in accordance with ISO 10993-18 or applicable pharmacopeia.

NOTE 2 The studies under 4.5.5 can be in addition to conformity with chemical characterization of the NIS according to ISO 10993-18 and the determination of allowable limits for substances leachable from medical devices according to ISO 10993-17, organic and inorganic chemical entities which can be required under ISO 11608-1.

4.5.6 Sterilization of the reservoir and/or integrated fluid path

The reservoir and/or integrated fluid path shall be sterilized by a validated process to a Sterility Assurance Level (SAL) of 1×10^{-6}. A higher SAL (e.g. 1×10^{-3}) may be justified through risk assessment. The need for a higher SAL requires consideration of the individual situation, including consideration of the risk assessment undertaken by the manufacturer of the medical device.

The sterile barrier shall be evaluated for sterile barrier integrity;

— after simulated shipping conditioning;

— at the end of the designated shelf life.

If the entire reservoir and/or integrated fluid path is a sterile subassembly of the NIS, that subassembly may serve as the sterile packaging (e.g. hermetically sealed housing) and shall conform to the requirements of ISO 11607-1 for sterile packaging.

Sterility of the medicinal product as delivered to the patient can be ensured through the following, obviating the need for additional medical product sterility testing after delivery;

— verification of the sterility of the medicinal product as supplied in its PCC;

— verification of the sterility and integrity of the fluid path before use;

— verification of the fluid path remains integral during use through assessment of leakage in accordance with 4.6.

NOTE It is not necessary to perform sterility testing on medicinal product that is delivered by the NIS as this type of testing would be very sensitive to technique and likely result in false positives.

With a pre-filled NIS that is designed such that the medicinal product is to be transferred from a sterile PCC and a sterile fluid path through non-sterile surfaces (e.g. external surface of a cartridge disc), it shall be ensured that the risk of contamination of the medicinal product during the transfer process is adequately controlled.

4.6 Medicinal product leakage

All containers and fluid paths shall be assessed for leakage when tested for primary function in accordance with ISO 11608-1, in environments and orientations representative of the expected use. Any amount of leakage observed external to the NIS during testing shall be assessed for its ability to impact device performance, fluid path or medicinal product sterility, or risk to humans or the environment. Any allowable leakage shall be addressed by risk assessment and appropriate information shall be provided to the user in the instructions for use.

NOTE The impact of leakage on the function of the NIS can be assessed through dose accuracy testing.

If any preconditioning creates the appearance of condensation or any other external evidence of fluid, it shall be assessed and confirmed that this was not medicinal product leakage.

5 Test methods

5.1 Resealability for multi-dose cartridges or reservoirs

The largest outer diameter needle provided or listed/recommended in the NIS instructions for use shall be used. If the needle gauge is unknown, a 29gauge needle shall be used unless a risk assessment suggests otherwise. A new needle shall be used for each penetration unless otherwise indicated in the instructions for use of the NIS.

The penetrations shall be performed in a manner consistent with its use in the NIS. For example, a pen-injector cartridge should be punctured while held in the cartridge holder of a prefilled NIS or a fully assembled reusable NIS before puncturing. The disc shall be punctured by attaching the needle as defined in the instructions for use of the NIS.

For the last needle penetration of each cartridge or reservoir, a dose shall be expelled equivalent to the maximum dose size for the NIS or a larger volume sufficient to move the plunger from its manufactured position and to remove air bubbles in the container.

After completing the number of penetrations determined in accordance with 4.2.2 and final dose expulsion, remove the needle, wipe the disc to remove any liquid which might be present, place each cartridge or reservoir in the test fixture, and exert a test force (F) as determined by the following formula (or as specified by a risk assessment):

$$F = 0{,}106 \times d^2$$

where d is the nominal inside diameter of the container.

The test force shall be applied to the plunger closest to the disc for not less than 60 s. Wipe the disc surface with a clean blotter immediately after application of the test force to determine evidence of leakage.

The formula above establishes a force requirement based on traditional cartridges which were required to have a sustaining force of less than 10 N. If the risk assessment identifies that the cartridge might be subjected to a higher force during use, for example a dual plunger system, the test force to simulate use conditions shall be adjusted.

Resealability assessments for other container geometries should follow the principles established in example given in NOTE 1.

NOTE 1 It is impractical to address test methods for all potential container geometries beyond cartridges for the assessment of container-needle interface robustness against user interactions that puncture the seal multiple times during use (assessment of container resealability after the fluid path is established and then removed). Therefore, as an example, only specific requirements unique to multi-dose cartridge-based containers or reservoirs with discs are presented.

NOTE 2 See also Annex C for further information.

5.2 Fragmentation (disc coring) – cartridges or reservoirs

Test cartridges or reservoirs in the condition in which they will be used. The number of cartridges or reservoirs selected should permit a minimum of 100 punctures to be performed. The minimum number of cartridges or reservoirs to be used is 5.

For example:

— if each cartridge or reservoir is to be punctured one time, select 100 samples;

— if each cartridge or reservoir is to be punctured 10 times, select 10 samples;

— if each cartridge or reservoir is to be punctured 100 times, select minimum 5 samples.

For multi-dose cartridges or reservoirs, a new needle (or whatever access device is specified in the NIS instructions for use) shall be used for each penetration, unless otherwise indicated in the NIS instructions for use.

The needles or access devices used for testing shall be those specified in the NIS instructions for use. Where multiple needles and/or access devices are specified, the test shall be conducted with each specified needle and access device unless the manufacturer justifies that the needles and/or access devices used for testing are representative of the range of those specified.

For single-dose cartridges, perform the number of penetrations determined in accordance with 4.2.3.

For multi-dose cartridges or reservoirs, perform the number of penetrations determined in accordance with 4.2.3. The penetrations shall be performed in a manner consistent with use in the NIS. For example, a pen cartridge shall be punctured while held in the cartridge holder, or fully assembled into the NIS if provided prefilled or required to be loaded into the NIS before puncturing.

After each puncture, purge the needle/access device and/or integrated fluid onto a filter with a pore size of approximately 5 µm using particle-free water.

After the requisite number of piercings, empty the cartridge or reservoir contents onto a separate filter of the same pore size. Emptying of cartridge or reservoir may be combined with purging of needle/access device and/or integrated fluid path for the NIS where these cannot be removed from the NIS.

Perform the water rinsing and particle count procedure according to the membrane filtration procedure in applicable pharmacopeia.

NOTE See Annex A.

The total number of particles from all filters shall not exceed the requirements in 4.2.3.

5.3 Sub-visible particulates

Prepare a test sample by filling or flushing the reservoir and/or integrated fluid path of 10 NISs with particle-free water in accordance with applicable pharmacopeias (using the filling device and/or mechanism specified in the instructions for use) into a container rinsed with particle-free water.

Prepare a control sample (using the same filling device and/or mechanism specified in the instructions for use) to expel particle-free water into an appropriately cleaned container.

Enumerate the sub-visible particulate matter content of the reservoir and/or integrated fluid path in accordance with applicable pharmacopeias. The number of particulates is the difference between the test samples and control.

5.4 Visible particulates

Prepare a test sample by filling or flushing the reservoir and/or integrated fluid path of 10 NISs with particle-free water in accordance with applicable pharmacopeias (using the filling device and/or mechanism specified in the instructions for use) into a container rinsed with particle-free water.

Prepare a control sample (using the same filling device and/or mechanism specified in the instructions for use) to expel particle-free water into an appropriately cleaned container.

Visually inspect for the presence of visible particulates (diameter ≥150 µm) in the test sample as compared to the control.

6 Information supplied with the container

6.1 General

The requirements in ISO 11608-1:2022, 12.1 shall apply.

6.2 Marking on the unit packaging

The requirements in ISO 11608-1:2022, 12.2 shall apply.

In addition, where appropriate, the word ‘STERILE’ or the symbol ISO 7000-2499 and the method of sterilization shall be included on the unit packaging.

Annex A
(informative)

Medicinal product compatibility references – Requirements, guidance, standards or compendia material

Table A.1 provides reference to some requirements, guidance, standards or compendia material for each requirement listed in Clause 4.

Table A.1 — Medicinal product compatibility references

Item	Reference	Comment
Particulates - Visible	Pharmacopoeia standards (USP, PhEur, JP)	ISO 8536-4 USP<790>
Particulates - Visible - Fragmentation	Pharmacopoeia standards (USP, PhEur, JP)	USP<382> Manufacturer and customer to agree on test method
Particulates - Subvisible	Pharmacopoeia standards (USP, PhEur, JP)	USP <788> (or Eur. Ph. 2.9.19, which is harmonized with other pharmacopoeia) Use a methodology similar to ISO 8536-4
Biocompatibility/biological reactivity	ISO 10993-1	FDA Draft Guidance: Use of ISO 10993-1
	EMEA Guideline on Plastic Immediate Packaging Materials (CPMP/QWP/4359/03-EMEA/CVMP/205/04)	
	USP <87> Biological Reactivity Tests – In vitro; USP <88> Biological Reactivity Tests – In vivo	
	USP <1031> The Biocompatibility of Materials Used in Drug Containers, Medical Devices and Implants	
Pyrogenicity – endotoxin mediated	FDA Guidance for Industry Pyrogen and Endotoxins Testing: Questions and Answers - includes the following references: - AAMI/ANSI ST72 concerning "Bacterial endotoxins - Test methods, routine monitoring, and alternatives to batch testing" - US Pharmacopeia USP <85> (essentially identical to the European Pharmacopeia EP 2.6.14)- US Pharmacopeia USP <161>Transfusion and Infusion assemblies and Similar Medical Devices and/or to "FDA Guidance for Industry Pyrogen and Endotoxins Testing: Questions and Answers" (Acceptable limits for the control of endotoxins)	

Table A.1 *(continued)*

Item	Reference	Comment
Pyrogenicity – material mediated	Pyrogenic compound could be the source of systemic toxicity as described in ISO 10993-11 and need to be tested at device level. ISO 10993-11 refers to rabbit pyrogen test per Pharmacopeia for test method.	
Extractable/leachables	EMEA/CHMP/QWP/251344/2006: Guideline on the limits of genotoxic impurities	
	ISO 10993-18	
	ISO 10993-17	
	CHMP/CVMP. Guideline on Plastic Immediate Packaging Materials. European Medicines Evaluation Agency)	
	PQRI (Product Quality Research Institute) document: Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled Drug Products	PQRI PODP Recommendations forthcoming: Safety Thresholds and Best Practices for Extractables and Leachables in Parenterals and Ophthalmic Drug Products
	ISO 10993-12	
	Extractable methods are documented in USP <661> (Glass, PE, PP, PET, PETG), USP <381> Elastomeric Closures for Injections. Toxicology Testing is covered in USP <87> Biological Reactivity Tests – In vitro; USP <88> Biological Reactivity Tests – In vivo; <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems. Leachables are addressed in <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems Requirements from European Pharmacopeia around materials include Pharm Eu 3.1 Materials Used for the Manufacture of Containers and Pharm Eu 3.2 Containers.	Additional chapters forthcoming from USP: i. <661> Plastic Packaging Systems and their Materials of Construction a. <661.1> Plastic Materials of Construction b. <661.2> Plastic Packaging Systems for Pharmaceutical Use
Sterility	ISO 17665-1 ISO 11135 USP 27, Sterility, Biocompatibility, Biological Tests and Assays, Bacterial Endotoxin Test (LAL), Pyrogen Test (USP Rabbit Test), or other applicable tests related to the drug/biological product and delivery of the drug/biological product ISO 11137-1 ISO 11737-2	Such standards referenced in: FDA Guidance for Industry: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products
	ISO 11607-1	

Table A.1 *(continued)*

Item	Reference	Comment
Stability/shelf life testing	ICH Q1A(R2) Stability Testing of New Drug Substances and Products FDA Guidance: Shelf Life of Medical Devices	
	ASTM F1980- Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices ASTM D3045- – Standard Practice for Heat Aging of Plastics Without Load	Approaches to perform accelerated aging.
Container/closure integrity	FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics .	Referenced in: FDA Guidance for Industry: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products
	ICH Q8(R2) Pharmaceutical Development	

Annex B
(informative)

Historical references to previous editions

Tables B.1, B.2, B.3 and B.4 provide information about critical dimensions and details on measurement methods drawn from former editions of this document (ISO 11608-3:2012 and ISO 11608-3:2000). In previous editions, the critical dimensions specified provided a useful baseline specification for design of "Type A" cartridges intended for use with NIS. This document does not specify specifications for the design of a Type A cartridge, as it has a broader scope than just cartridges.

The following cartridge information was extracted from ISO 11608-3:2012, Clauses 4 and 5.

Table B.1 — Extracted from ISO 11608-3:2012, 3.14

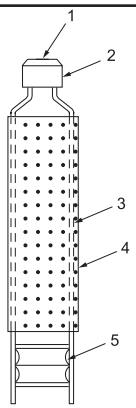
Extracted Clause/Figure/Table	Remarks
 **Key** 1 disc 2 cap 3 cylinder 4 label 5 plunger **Figure 1 — Finished cartridge**	

Table B.2 — Extracts from ISO 11608-3:2012, Clause 4

Extracted Clause/Figure/Table	Remarks
4.3.2 Cartridges The initiating force for cartridges shall not exceed 15 N, when tested in accordance with the test method given in 5.4. The sustaining force for cartridges shall not exceed 10 N, when tested in accordance with the test method given in 5.4.	The title of 4.3: Plunger force

Table B.2 *(continued)*

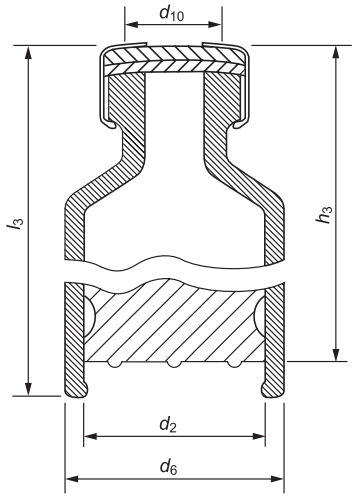
Extracted Clause/Figure/Table	Remarks
4.4.2 Cartridges For cartridges, the dimensions l_3 and h4 shall be measured in accordance with the test method in 5.6.1 and 4.5.2, respectively. Dimensions d6 and h3 shall be measured in accordance with the test method in 5.6.2.  NOTE The dimensions given are the minimal dimensions that should be identified for cartridges. There may be additional relevant dimensions to be identified for a particular system. **Figure 2 — Finished cartridge dimensions**	The title of 4.4: Dimensions In ISO 11608-3:2012, no dimensions were specified. In ISO 11608-3:2000, the dimensions were given in Table 1 (see Table B.3).
4.5.2 Cartridges For cartridges, the maximum eccentricity shall be determined in accordance with the test method in 5.6.3.	The title of 4.5: Eccentricity This sub-clause dimension d_6 is to be measured with label in place and at label overlap.

Table B.3 — Extracted from ISO 11608-3:2000, Clause 4

Extracted Clause/Figure/Table	Remarks
Table 1 — Dimensions of Type A finished cartridges **Dimensions in millimeters** See table below.	In ISO 11608-3:2000, maximum dimension h_3 was revised to be for reference only and is manufacturer specified.

Dimension	1,5 ml cartridge		3 ml cartridge	
	dimension	tolerance	dimension	tolerance
l_3	58,70	±0,30	63,90	±0,30
d_6	8,94	max.	11,94	max.
h_3	0,20	min.	0,20	min.
d_2[a)]	6,85	±0,10	9,65	±0,10
Eccentricity	0,33	max.	0,33	max.

[a] As specified in ISO 13926-1.

Table B.4 — Extracts from ISO 11608-3:2012, Clause 5

Extracted Clause/Figure/Table	Remarks
5.4 Plunger force Measurements shall be made at a test speed of 50 mm/min with test cartridges that are open to the atmosphere (i.e. no septum present, fluid to be removed immediately prior to testing), so that only the plunger friction is measured. The initiating force is the peak force seen at the start of the plunger movement. The maximum sustaining force is measured over the measurement zone, which comprises not less than 75 % of cartridge deliverable volume.	
5.6.1 Length reference, l_3 Measure the distance from the bottom of the cylinder to a line perpendicular to the axis of the cylinder which goes to a reference mark on d_{10} (as shown in Figure 2) made on the cap. This reference mark is representative of an interface to the NIS. EXAMPLE Reference mark could be located on d_{10} of 5 mm.	The title of 5.6: Dimensions Sub-clause 5.6.1 dimension d_{10} is recommended to be 5 mm, although not explicitly stated in the section.
5.6.2 Overall diameter, d_6 and plunger insertion depth, h_3 Measure the maximum diameter for d_6 and the maximum length for h_3.	The title of 5.6: Dimensions
5.6.3 Eccentricity (attribute) Measure the maximum eccentricity between the cap centreline and the centreline of the finished cartridge outside diameter (d_6, at label overlap) by recording the total indicated run out (TIR) and dividing the result by two. NOTE Control of eccentricity is important to minimize side-loading of the cap when placed in the NIS. It also facilitates centring of the disc for needle attachment.	The title of 5.6: Dimensions

Annex C
(informative)

Theoretical support for resealability requirements

C.1 General

ISO 11608-3:2012, 5.6.5 on resealability testing, recommended the preparation of a sample by performing consecutive needle penetrations of the disc followed by the application of a 5 N force to the plunger for a period of time. The theory was that the force applied to the plunger would pressurize the cartridge thereby testing the disc robustness against leakage after multiple needle punctures typical of device use. Two challenges existed for the resealability test relative to the application force:

a) the reduction of internal container pressure due to the plunger initiation force and its impact on plunger movement;

b) the impact of cartridge diameter on the internal container pressure generated by any given application force.

These challenges are addressed in this document.

C.2 The reduction of internal container pressure due to limited plunger movement

In theory, a force applied to the plunger (input force) is converted to an internal container pressure (output force). This relationship is modelled by the following formula:

$$P = F / A$$

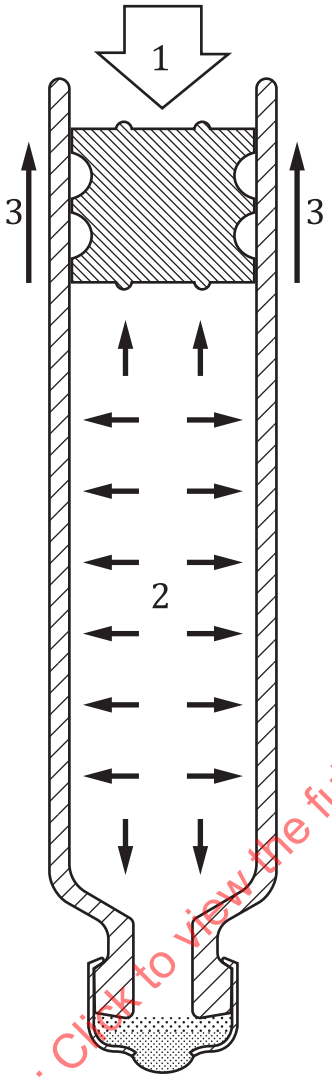
where

P internal pressure of the container; measured in N/mm^2

F force applied to the container plunger; measured in N

A area of the face of the plunger exposed to the fluid within the container; measured in mm^2

In practice, the internal pressure is less due to the frictional forces acting on the plunger reducing the effective applied force (see Figure C.1).



Key

1 application force

2 internal pressure, $P = F / A = \left(F_{\text{applied}} - F_{\text{friction}}\right) / A$

3 frictional force component ($F_{\text{breakloose}}$ *or* $F_{\text{sustaining}}$)

Figure C.1 — Cartridge pressurization after the application of a plunger force

The cartridge cannot be pressurized for resealability testing until the plunger frictional forces (breakloose and sustaining) are overcome such that the plunger leading face can move forward. Since the container liquid has low compressibility, just enough plunger movement to allow the plunger face to bow might be sufficient to pressurize the cartridge. However, the presence of an air bubble within the container will add a compressible element that will require greater plunger movement to obtain an adequate internal pressure.

To address this issue, this document adds a step to the sample preparation that includes a dose volume expulsion after the last needle penetration that will serve to remove any air present in the container and move the plunger enough to eliminate the breakloose frictional force. In addition, the application force will be increased from 5 N to 10 N to overcome the typical sustaining force.

NOTE The limit on sustaining force in ISO 11608-3:2012 was 10 N.

C.3 The impact of the cartridge diameter on the internal container pressure generated by any given application force

If the application force is constant while the internal container diameter (d) varies, the internal container pressure will also change as a function of the inverse of the container internal diameter squared:

$$P = F / A$$

$$P = F / \left(\pi \times \left(\frac{d}{2} \right)^2 \right)$$

$$P = \left(F / d^2 \right) \ (4 / \pi)$$

ISO 11608-3:2012, 5.6.5 would allow for a less challenging resealability test as the container internal diameter increases.

To address this, this document defines a target container pressure for the resealability, P_{target}, in N/mm^2, test using a nominal container internal diameter of 9,7 mm and an application force of 10,0 N:

$$P_{target} = \left(F / d^2 \right) \ (4 / \pi)$$

$$P_{target} = \left(10{,}0 / 9{,}7^2 \right) \ (4 / \pi)$$

$$P_{target} = 0{,}135$$

The target pressure is then used to define an equation used to calculate the application force required to yield the desired target pressure for any given container diameter:

$$F = P_{target} \times A$$

$$F = P_{target} \times \pi \times \left(\frac{d}{2} \right)^2$$

$F = P_{target} \times \pi / 4 \times d^2$ then using the target pressure determined above,

$$F = 0{,}135 \times \pi / 4 \times d^2$$

$$F = 0{,}106 \times d^2$$

When performing a resealability test with a 9,7 mm internal diameter container, apply the following force, F, in N, to the plunger:

$$F = 0{,}106 \times d^2 = 0{,}106 \times 9{,}7^2 = 10{,}0$$

When performing a resealability test with a 9,2 mm internal diameter container, apply the following force, F, in N, to the plunger:

$$F = 0{,}106 \times d^2 = 0{,}106 \times 9{,}2^2 = 9{,}0$$

Annex D
(informative)

Reservoir and integrated fluid path leachables

D.1 General

D.1.1 Background

The purpose of reservoir and integrated fluid path leachables studies is to systematically and rationally quantify (i.e. characterize) and assess the impact of organic and inorganic chemical entities that might leach into the medicinal product (which will be delivered to the patient) to the extent practicable, and within certain defined analytical threshold parameters. The results of reservoir and integrated fluid path leachables studies are used in the overall leachables assessment to understand the potential effect of leachables on patient safety and medicinal product quality and stability. Leachable chemicals can come from contact with the materials of the Primary Container Closure (PCC) during storage or through contact with device materials during transfer and delivery. Extractables and leachables from the PCC are not addressed in this document. This document only addresses those extractables and leachables that come from contact with the reservoirs and integrated fluid path of the NIS to assess the potential risk they pose to the patient in relation to the benefit provided. If the risks exceed the benefits, then the risks should be mitigated.

D.1.2 Identification of extractables (pre-requisite for leachables)

Extractables are organic and inorganic chemical entities that can be released from the reservoir and/or fluid path into an extraction solvent under laboratory conditions. Extractables themselves, or substances derived from extractables, have the potential to leach into a medicinal product under normal conditions of storage and use and become leachables.

An extractables study of the reservoir and/or integrated fluid path should be performed as a means to inform the reservoir and integrated fluid path leachables study by identifying the potential substances that could be leached. The conditions (solvents, times and temperatures) of the extractables studies, whether performed according to ISO 10993-18, or according to the relevant pharmacopeia, should be guided by risk assessment and consider the properties of the medicinal product, the materials of construction of, and fluid path and duration of contact between, the medicinal product and the reservoir and/or fluid path. These laboratory conditions (e.g. solvent, temperature, stoichiometry, etc.) can accelerate and/or exaggerate the normal conditions of storage and use. The results from these studies enable development of targeted methods for leachables identification and evaluation.

D.1.3 Leachables

Leachables are organic and inorganic chemical entities that are present in the medicinal product as delivered from the fluid path because they have leached into the medicinal product from reservoir and/or fluid path under normal conditions of use. Because leachables are derived from the reservoir or fluid path, they are not related to either the medicinal product itself or its vehicle and ingredients. Leachables are typically a subset of extractables or are derived from extractables.

The purpose of a leachables study is to systematically and rationally identify and quantify (i.e. characterize) to understand the impact of leachables on patient safety to assess the potential risk they pose to the patient in relation to the benefit provided. Limits should be established for leachables in accordance with ISO 10993-17. If the risks exceed the benefits, then the risks should be mitigated.

Data should be collected to determine the identity and quantity of compounds that leach into the medicinal product from the reservoir and/or fluid path. These studies should include in-use testing

where doses as delivered from the system are evaluated. If there is a risk of change in material properties or degradation of the materials of the reservoir or fluid path over time with potential to impact leachables, testing should be repeated at the end of NIS lifetime (this can be done by accelerated aging, if appropriate). Changes or degradation in material properties could impact the observed leachables as these changes might indicate differences in surface or molecular structure of the material, and therefore might influence the likelihood or rate that a given substance is capable of leaching into the drug product (e.g. surface changes, degradation of coatings, molecular weight changes, tensile strength changes).

D.1.4 Leachables methods

Suitable methods for evaluating leachables should be developed and validated, taking into account the potential extractables that were observed in the extractables studies. The methods should be capable of performance at an appropriate quantitation level. This quantitation level is derived by considering the dose parameters for a given medicinal product per the medicinal product's label claim and leachables limits (established in accordance with ISO 10993-17). The method quantitation level is converted from units of exposure (i.e. µg/day) to units of concentration (e.g. µg/ml, µg/g, µg/canister, µg/vial, etc.) to facilitate laboratory analysis.