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Transfer sets for pharmaceutical preparations — Requirements and test methods

Ensemble de transfert pour préparations pharmaceutiques — Exigences et méthodes d'essai

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Foreword

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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).

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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 76, *Transfusion, infusion and injection, and blood processing equipment for medical and pharmaceutical use,* 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 22413:2010), which has been technically revised.

The main changes compared to the previous edition are as follows:

— the structure (moving all tests to the new Annex A) and partly the content were aligned with ISO 8536-4;

— Table 1 on penetration force was amended by a new entry;

— 6.7 (formerly 5.7) on fragmentation was clarified;

— former Clause 12 on storage was deleted;

— Clause 10 (formerly Clause 13) on labelling was updated;

— Clause 11 on the disposal has been added due to the single-use character of the product;

— former Annexes A and B on testing of fragmentation of transfer sets were moved to a new Annex A on physical tests;

— most of the tests in Annex A were, as far as necessary, aligned with the appropriate tests in ISO 8536-4;

— a new Clause A.9 on a test for stress cracking of small-bore connectors was added;

— Clause 2 and the Bibliography were updated.

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

Transfer sets for pharmaceutical preparations transmit fluids from one container to another. The transfer sets mix fluids or dissolve dry substances and are used in combination with infusion and injection containers.

The transfer sets consist either of two piercing devices or of a piercing device in combination with a small-bore connector, which can be connected with each other in different ways. Transfer sets can have a housing.

Examples of different designs:

a) two piercing devices connected to each other (similar to piercing devices of infusion containers);

b) a metal cannula, bevelled on both sides or a combination of a) and b);

c) metal cannulae, mostly having a hub or a grip plate in the middle, fixed to the plastic part;

d) plastic piercing devices directly connected to a grip plate, or held by a tube at a distance to allow a higher hydrostatic pressure;

e) piercing devices with an additional ventilation channel that can end in the other tip or outside;

f) piercing devices with an air filter;

g) piercing device in combination with a small-bore connector;

h) piercing device in combination with a small-bore connector and a particle filter;

i) piercing devices with housings serving, among other things, as a guide and a fixation on the connected containers for a secure, injury-free and contactless application.

Transfer sets for pharmaceutical preparations — Requirements and test methods

1 Scope

This document specifies requirements and test methods for sterilized single-use transfer sets that are used for pharmaceutical preparations.

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 8362 (all parts), — *Injection containers and accessories*

ISO 8536 (all parts), — *Infusion equipment for medical use*

ISO 8871-5, *Elastomeric parts for parenterals and for devices for pharmaceutical use — Part 5: Functional requirements and testing*

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

ISO 15223-1, *Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied — Part 1: General requirements*

ISO 15747, *Plastic containers for intravenous injections*

ISO 15759, *Medical infusion equipment — Plastics caps with inserted elastomeric liner for containers manufactured by the blow-fill-seal (BFS) process*

ISO 80369-1, *Small-bore connectors for liquids and gases in healthcare applications — Part 1: General requirements*

ISO 80369-20:2015, *Small-bore connectors for liquids and gases in healthcare applications — Part 20: Common test methods*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

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

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

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

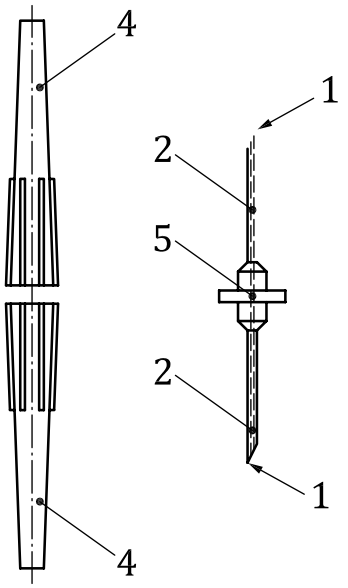
3.1
transfer set
medical device to transmit liquid pharmaceutical preparations from one container to another

Note 1 to entry: The transfer set mixes fluids or dissolves dry substances and is used in combination with infusion and injection containers.

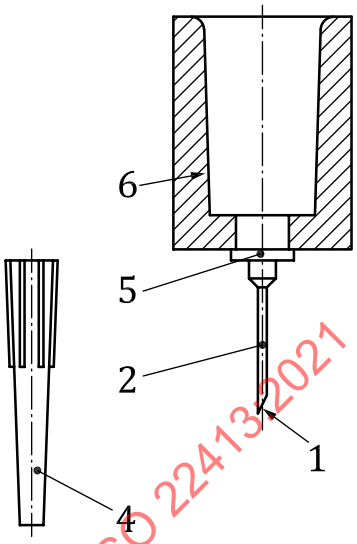
4 Design and designation

4.1 Design for transfer sets without housing

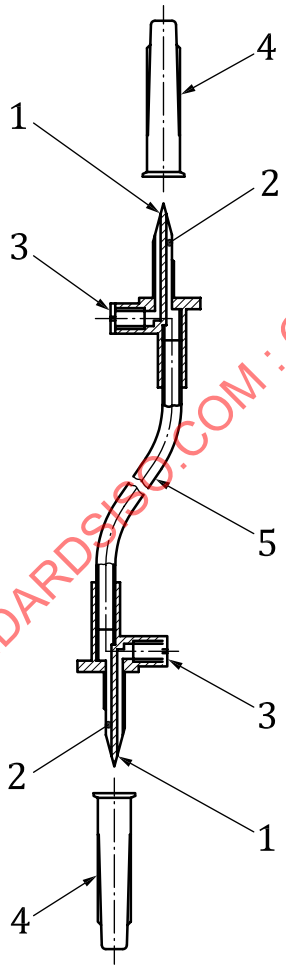
The designs of the individual components are given in Figure 1 and Figure 2. The Figures serve as examples of possible transfer sets. Other designs are acceptable.



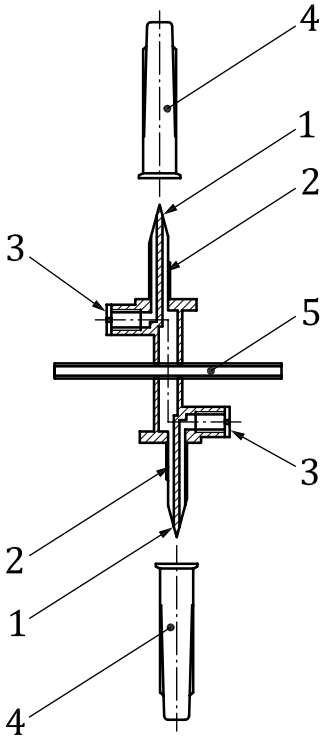
a) Transfer set with one channel



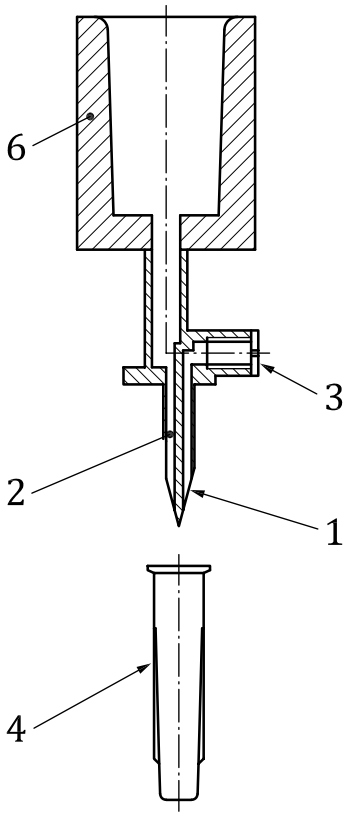
b) Transfer set with one channel in combination with a small-bore connector



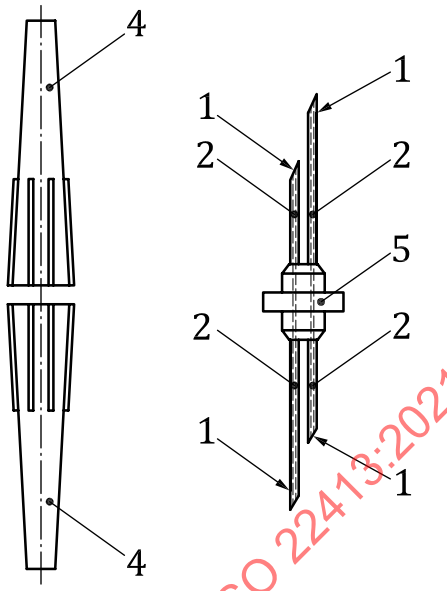
c) Transfer set with an air inlet/air outlet



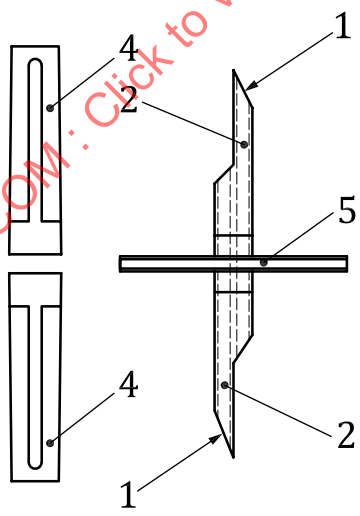
d) Alternative transfer set with an air inlet/air outlet



e) Transfer set with an air inlet/air outlet in combination with a small-bore connector



f) Transfer set with two channels



g) Alternative transfer set with two channels

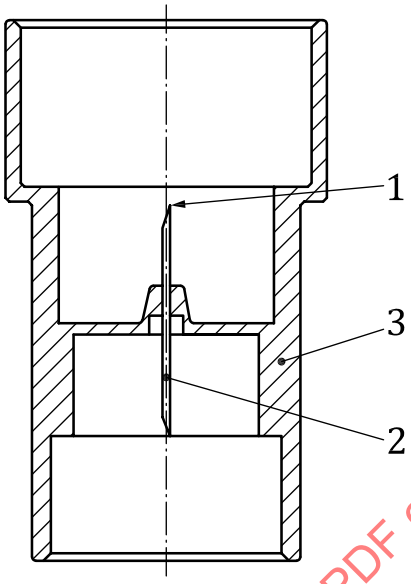
Key

1 piercing device
2 channel
3 channel with air filter for ventilation, optionally lockable
4 protective cap
5 connection of piercing devices by hub, grip plate or tube
6 small-bore connector

Figure 1 — Transfer sets without housing

4.2 Design for a transfer set with housing

The design of a transfer set with housing is given in Figure 2. The drawing serves as an illustration of a possible transfer set with housing. Other designs are acceptable.



Key

1 piercing device
2 channel
3 housing

Figure 2 — Transfer set with housing

4.3 Designation

Designation shall follow label requirements according to Clause 10.

5 Materials

The materials for the transfer sets and their individual components shall conform to the requirements in Clause 6. If the components are exposed to the liquid to be transferred, the chemical and biological requirements in ISO 8536-4 shall be met.

Piercing devices shall be manufactured from appropriate materials, e.g. metal and/or plastic.

6 Physical requirements

6.1 Particulate contamination

Transfer sets shall be manufactured under conditions that minimize particulate contamination. All parts shall be smooth and clean at the fluid pathway surfaces. When tested as specified in A.2, the number of particles shall not exceed the contamination index limit.

6.2 Tensile strength

6.2.1 When tested as specified in A.3 the transfer set shall withstand a static tensile force of not less than 15 N for 15 s.

6.2.2 When using metal piercing devices connected to plastic parts, the bond shall conform to ISO 7864.

6.3 Leakage

The transfer set shall be airtight, no leaks of air or liquid shall occur when tested in accordance with A.4. Sterility shall be maintained.

6.4 Free flow

When tested in accordance with A.5, a free flow of air and/or liquid shall be ensured.

6.5 Piercing device

The piercing devices shall be suitable for penetration of the intended closure system for injection and/or infusion containers made of glass or plastic. After puncture, a free flow shall be ensured. When tested in accordance with A.6, the surface of the piercing devices shall be smooth and free of burrs.

The maximum outer diameter of the piercing device shall be ≤6,5 mm.

6.6 Penetration force

When tested in accordance with A.7, the penetration forces determined in Table 1 shall not be exceeded.

Table 1 — Penetration force

Type of piercing device	Penetration force N max.	Counterpart
Transfer sets with metal piercing device	10	Injection closures ISO 8362-2 – 20 – A Hardness: 40 Shore A to 55 Shore A
Transfer sets with plastic piercing device	80	Infusion closures ISO 8536-2 – 32 – A Hardness: 40 Shore A to 55 Shore A
Transfer sets with plastic piercing device	200	Plastic containers for intravenous injections ISO 15747
NOTE Freeze-drying closures (FD closures) can have tight channels at the bottom, which considerably affect the penetration force.		

6.7 Fragmentation

Transfer sets have, in general, multiple piercing devices. During testing and evaluation, each piercing device shall be considered individually.

Piercing devices are intended to be used to pierce closure systems, which can result in fragmentation. Fragments are particles – unintentionally generated while puncturing the closure system by means of the piercing device – that block the channel of the piercing device or may fall into the pharmaceutical preparation.

The design of the piercing devices shall aim to avoid fragments being emitted during piercing. It shall be designed so as to minimize coring and fragmentation when penetrating vial closures.

This document does not specify requirements or test methods for these properties, but an example of a test method for determining the unintentional generation of fragments from rubber closures is given in A.8.

6.8 Air inlet and air outlet

Transfer sets containing an air inlet with air filter shall maintain sterility of the fluid path.

The air filter should be hydrophobic.

6.9 Protective caps

Where used, the protective caps shall cover the respective surfaces of the transfer device to prevent contamination from surrounding environment, to avoid stick injuries and packaging damages. Protective caps shall be secure but easily removable.

6.10 Transfer sets with housing

6.10.1 Transfer sets with housing shall be designed in order to conform with the applicable part of the ISO 8362 series and the applicable part of the ISO 8536 series as well as to conform with ISO 15747 and ISO 15759.

6.10.2 Transfer sets with housing shall be designed in a manner that injury or contact with cannulae is prohibited by the housing, the protective caps or by suitable packaging.

6.11 Small-bore connectors

Where applicable, small-bore connectors shall conform to ISO 80369-1. For stress cracking test, see A.9.

6.12 Fluid filter

Fluid filters, if integrated, shall conform to the requirements for particle retention according to ISO 8536-4.

7 Chemical requirements

The requirements of ISO 8536-4 shall be met.

8 Biological requirements

The requirements of ISO 8536-4 shall be met.

9 Packaging

The transfer sets shall be packed so that the sets remain sterile during storage. The unit container shall be sealed in a tamper-evident manner. Packaging shall be in accordance with ISO 11607-1.

The transfer sets shall be packed and sterilized so that there are no flattened portions or kinks that limit the performance of the devices when they are ready for use.

10 Labelling

10.1 General

The labelling shall include the requirements as specified in 10.2 and 10.3. If graphical symbols are used, then refer to ISO 3826-2 and ISO 15223-1.

NOTE The presence of substances of interest can be indicated by using symbol ISO 7000-2725 and replacing the "XXX" by the abbreviation of the substance. The absence of substances of interest can be indicated by crossing the respective symbol.

10.2 Unit container

The unit container shall be labelled at least with the following information using the graphical symbols in accordance with ISO 15223-1, where appropriate:

a) name and address of the manufacturer;

b) description of the contents;

c) indication that the transfer set is sterile;

d) lot (batch) designation;

e) year and month of expiry;

f) indication that the transfer set is for single use only, or equivalent wording;

g) instructions for use, including warnings, e.g. about detached protective caps;

h) indication that the transfer set is non-pyrogenic, or that the transfer set is free from bacterial endotoxins.

If the available space is too small to give all this information in legible characters and/or symbols, the information may be reduced to d) and e). In this case, the information as required in this subclause shall be given on the label of the next bigger shelf or multi-unit container.

10.3 Shelf or multi-unit container

The shelf or multi-unit container, when used, shall be labelled at least with the following information using the graphical symbols in accordance with ISO 15223-1, where appropriate:

a) name and address of the manufacturer;

b) description of the contents;

c) indication that the transfer sets are sterile;

d) lot (batch) designation;

e) year and month of expiry;

f) recommended storage conditions, if any;

g) number of transfer sets.

11 Disposal

Information for a secure and environmentally sound disposal of single-use transfer sets should be given.

EXAMPLE "Always dispose of blood contaminated products in a manner consistent with established biohazard procedures."

Annex A
(normative)

Physical tests

A.1 General

All physical tests shall be performed at a temperature of (23 ± 2) °C unless other temperatures are given in the test method.

A.2 Test for particulate contamination

ISO 8536-4 shall apply.

A.3 Test of tensile strength

Expose the transfer set to be tested to a static tensile force of 15 N applied along the longitudinal axis for 15 s. Inspect whether the transfer set withstands the test force applied.

For metal piercing devices, the testing of the hub of the metal cannula shall be in accordance with ISO 7864:2016, Annex E.

A.4 Test for leakage

Seal the transfer set at one end. Apply an internal excess pressure of 50 kPa for 15 s using air at the open end, submerge it in water and determine whether air escapes. If the transfer set has two channels, both channels shall be tested.

Close the air inlet, if available, during testing.

A.5 Test for free flow

Inspect with a suitable method if the lumen is free of contractions that lead to a blockage of the transfer set.

A.6 Test of piercing device

Visually inspect if the surface of the piercing device is smooth and free from burrs.

Ensure the diameter conforms to 6.5.

A.7 Tests of penetration force

A.7.1 The piercing device shall be tested with the intended container/closure.

A.7.2 For metal piercing devices, testing shall be in accordance with ISO 8871-5.

A.7.3 For plastic piercing devices testing shall be in accordance with ISO 8536-2 and ISO 15747.

A.8 Testing on fragmentation

A.8.1 Plastic piercing devices

A.8.1.1 General

The test described below shall be used as a reference method for closure systems intended to be pierced with plastic piercing devices.

This test does not apply to piercing devices for injection closures.

A.8.1.2 Principle

The closure system of the containers for infusion or injection is pierced with a piercing device; the remaining fragments are collected and counted.

A.8.1.3 Apparatus

A.8.1.3.1 Ten infusion bottles, half-filled with filtered water, sealed with closure systems.

A.8.1.3.2 Devices for rinsing the particles out of the transfer set, e.g. disposable syringes.

A.8.1.4 Test samples and counterparts (see Table A.1).

Table A.1 — Test samples and counterparts

Test sample	Closure system	
	Marking	Requirement
Ten transfer sets with plastic piercing devices	Infusion closure ISO 8536-2 – 32 – A	Hardness: 40 Shore A to 55 Shore A

A.8.1.5 Pre-treatment

a) The plastic piercing devices are used without any pre-treatment.

b) The infusion closures are rinsed, sterilized and dried. Rinse twice using water at 60 °C in a glass. Sterilization is done in dry, saturated steam at (121 ± 1) °C for 30 min in an autoclave. Drying is done at a temperature of 60 °C for 60 min in a drying cabinet.

c) Sterilization serves as a simulation of the normal pre-treatment. In case of deviation due to a different method of application (e.g. sterilization by irradiation), it shall be stated in the test record.

d) The infusion bottles (A.8.1.3.1) are cleaned so that they contain no particles that would falsify the test result.

A.8.1.6 Procedure

The infusion closures are placed on infusion bottles, half-filled with filtered water and sealed with a crimp cap. Each infusion closure is pierced once with the piercing device inside the piercing area. After piercing, the plastic piercing device is rinsed out by injecting approximately 1 ml of water into the infusion bottle.

By swirling the infusion bottle with the piercing device, generated fragments are rinsed off. Crimp cap and infusion closure are removed from the infusion bottles; the content is successively filtered through a membrane filter (0,8 µm), while the infusion bottles are swirled gently to avoid sedimentation of fragments.