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Aerosol drug delivery device design verification — Requirements and test methods

Vérification de la conception d'un dispositif d'administration de médicament sous forme d'aérosol — Exigences et méthodes d'essai

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Foreword

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

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

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

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

ISO 20072 was prepared by Technical Committee ISO/TC 84, *Devices for administration of medicinal products and intravascular catheters*.

Introduction

This International Standard applies to hand-held aerosol drug delivery devices (ADDD) intended to administer medication to humans. To avoid unnecessarily restricting innovation, given the broad variation in device designs, this International Standard addresses the more general design/labelling requirements rather than specific physical and prescriptive design requirements. However, this International Standard does require the elaboration of a device functionality profile (DFP) specific to the ADDD in question. This International Standard also addresses ADDD design requirements from both the user interface and safety perspectives.

An ADDD is used as part of a system consisting of the ADDD, the container, the medication and the labelling, including the instructions for use. Therefore, design verification of the ADDD includes a final system verification test conducted in accordance with the instructions for use.

From a regulatory perspective, the ADDD system may be reviewed and approved as part of a drug product (combination of ADDD and medication) or as a device by itself. For the purposes of this International Standard, such regulatory distinctions do not alter the intent of the design verification process described herein. As an example, in the European Union (EU), if an ADDD is placed on the market in such a way that the ADDD and the medication form a single integral product (i.e. the system) that is intended exclusively for use in the given combination and which is not refillable, that single product shall be governed by Directive 2001/83/EEC. However, the relevant essential requirements of Annex I of the Medical Device Directive (93/42/EEC) shall apply as far as safety and performance-related ADDD features are concerned, which is the specific objective of this design verification standard.

Regardless of the distinctions (“drug” or “device,” pre-filled or refillable), it is recognised that ADDD design verification is an important component of the overall validation process. Moreover, design verification is iterative, to be conducted at various phases throughout the ADDD’s development and subsequent ADDD post-approval modifications. In all instances, design verification is conducted using the phase-appropriate instructions for use. It is understood that in the early phases of ADDD development an appropriate subset of the requirements contained herein might apply, but that all of the requirements will be satisfied as part of the final design verification exercise. Furthermore, design verification should be considered a minimum requirement for the safe and effective use of the ADDD, and in many instances additional testing may be appropriate as indicated by a risk assessment that shall also be conducted.

This International Standard introduces the requirement for developers and/or manufacturers to create a device functionality profile (DFP) for a given ADDD based on the ISO Standard for device risk assessment (as a part of ISO 14971). The device functionality profile defines the parameters and tolerance intervals used to verify the ADDD's ability to meet the manufacturer's design specifications during in-use conditions and following environmental and electromechanical extreme use conditions. This International Standard also includes a system verification test conducted at standard atmosphere and nominal flow rate as a simple bridge between the device design and the patient interface.

The purpose of this International Standard is to ensure a method and guide for independent testing of the repeatability and reproducibility of ADDD functionality that verifies compliance with its design specification. The design verification process may include use of applicable regulatory agency requirements and/or test methods. The sampling plans for this International Standard are intended to verify the design at a high confidence level. They do not replace the more general manufacturing quality systems, including lot release, which appear in standards on quality systems (e.g. the ISO 9000 series or ISO 13485).

Figure 1 illustrates the process this International Standard advises to use in order to assess and verify whether a design meets the determined DFP.

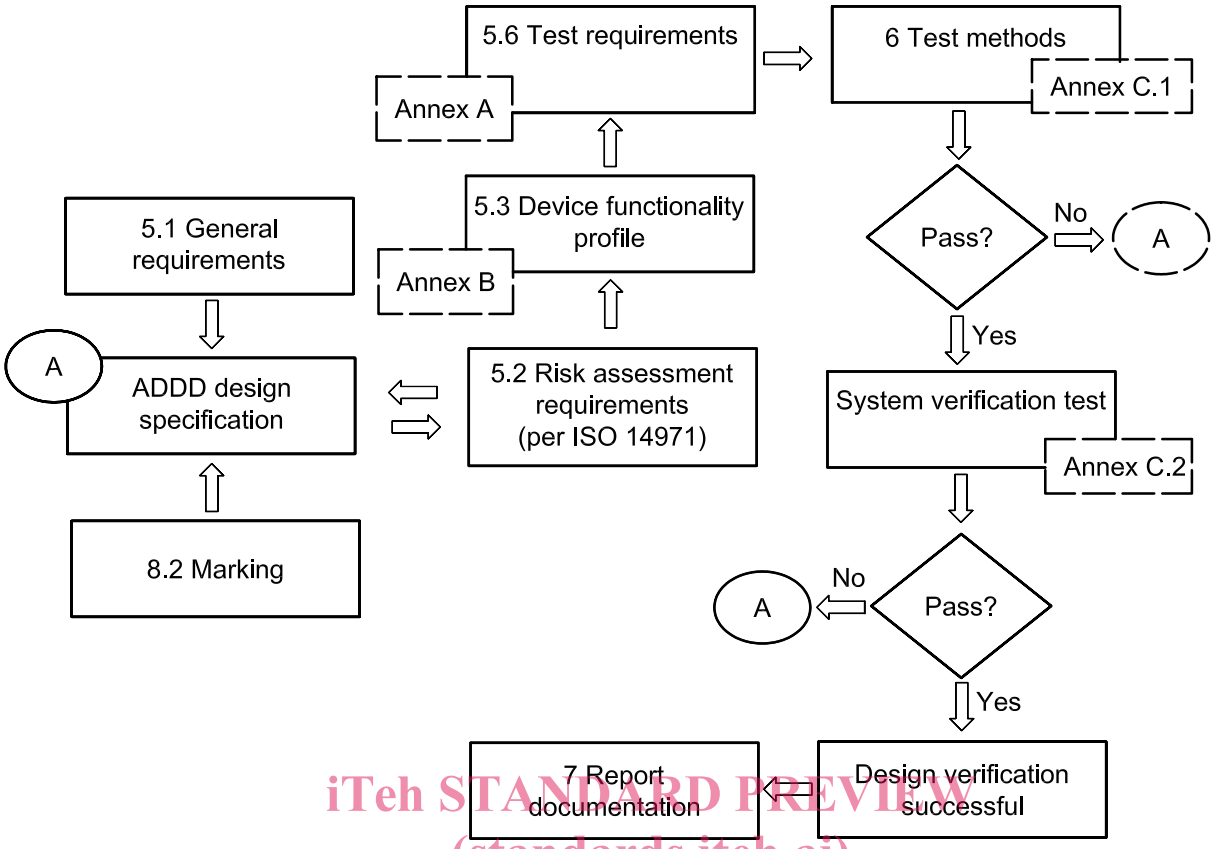

Figure 1 — ADDD design verification process

This International Standard specifically addresses the most basic elements regarding the safe and effective use of ADDD in humans. It does not define the pharmaceutical or clinical performance of an ADDD. Any labelling indicating ADDD use to deliver medication to specific regions of the respiratory tract falls under the authority of national governments or regional agencies regulating the manufacture and marketing of medical devices and pharmaceutical products. In some countries national regulations exist, and their requirements can supersede or complement this International Standard.

For a given manufacturer, existing marketed products and those currently under development might not fulfil some of the requirements. However, manufacturers should comply with this International Standard when improving the functional design of existing ADDDs or developing new ADDDs to obtain an even higher level of quality.

Annex A describes the reasoning for establishing the various requirements in this International Standard.

Aerosol drug delivery device design verification — Requirements and test methods

1 Scope

This International Standard applies to the design, labelling, instructions for use and testing requirements for hand-held single- and multi-use aerosol drug delivery devices (ADDDs) intended to deliver a metered or pre-metered aerosolized medication to or by means of the human respiratory tract (including nasal, oral, tracheal, bronchial and alveolar sites). This International Standard applies to both refillable and disposable devices intended for personal use.

This International Standard is intended for device design verification and not for drug product quality assessment. The objective of this International Standard is to verify, by laboratory (*in-vitro*) testing, that the ADDD design consistently meets the manufacturer's design specification by satisfying a device functionality profile and system verification test both of which are determined from a risk assessment and evaluated in accordance with the instructions for use.

This International Standard excludes continuous or semi-continuous aerosolization devices covered in ISO 27427, aerosolization devices which do not emit active pharmaceutical ingredient (API), general purpose aerosolization devices (for use with ventilators) and atomizers.

This International Standard does not apply to manufacturers of single parts or components of the ADDDs [e.g. (spray) pumps, valves, containers, etc.].

NOTE There might be times when a device falls under the scope of this International Standard and that of ISO 27427. The committee envisions that the intended use of the product and the risk assessment of the device will derive which International Standard the manufacturer chooses for design verification of the ADDD. This International Standard outlines the process by which ADDD design verification is to be performed in conjunction with a risk-based device functionality profile of the ADDD with either the medication, a placebo or a representative medication. ISO 27427 outlines the process by which the characterization of the aerodynamic aerosol performance of a nebulizing system for use with a non-specific class of active pharmaceutical ingredient(s) is made.

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 14971:2007, *Medical devices — Application of risk management to medical devices*

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing*

ISO 11135-1, *Sterilization of health care products — Ethylene oxide — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

ISO 11137 (all parts), *Sterilization of health care products — Radiation*

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

ISO 17665-1, *Sterilization of health care products — Moist heat — Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices*

IEC 60068-2-27, *Environmental testing — Part 2-27: Tests — Test Ea and guidance: Shock*

IEC 60068-2-30:2005, *Environmental testing — Part 2-30: Tests — Test Db: Damp heat, cyclic (12 h + 12 h cycle)*

IEC 60068-2-32, *Environmental testing — Part 2: Tests. Test Ed: Free fall*

IEC 60068-2-64, *Environmental testing — Part 2-64: Tests — Test Fh: Vibration, broadband random and guidance*

IEC 60601-1, *Medical electrical equipment — Part 1: General requirements for basic safety and essential performance*

IEC 60601-1-2, *Medical electrical equipment — Part 1-2: General requirements for basic safety and essential performance — Collateral standard: Electromagnetic compatibility — Requirements and tests*

IEC 60601-1-8, *Medical electrical equipment — Part 1-8: General requirements for basic safety and essential performance — Collateral standard: General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems*

IEC 60721-3-7, *Classification of environmental conditions — Part 3-7: Classification of groups of environmental parameters and their severities — Portable and non-stationary use*

IEC 61000-4-2, *Electromagnetic compatibility (EMC) — Part 4-2: Testing and measurement techniques — Electrostatic discharge immunity test*

IEC 61000-4-3, *Electromagnetic compatibility (EMC) — Part 4-3: Testing and measurement techniques — Radiated, radio-frequency, electromagnetic field immunity test*

IEC 62304, *Medical device software — Software life-cycle processes*

IEC 62366, *Medical devices — Application of usability engineering to medical devices*

3 Terms and definitions

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

3.1
accessory
add-on device (specifically referenced in the ADDD instructions for use) that may be used in conjunction with an ADDD to enable or enhance its performance

EXAMPLE Spacers, holding chambers, actuation counters, content indicators, etc.

3.2
active pharmaceutical ingredient
API
molecule(s) responsible for producing the intended therapeutic action

3.3
actuation
operation of the ADDD to release medication that will be aerosolized

NOTE The actuation can consist of the loading and release of the medication or only the release of the medication.

3.4
actuation counter
dose counter
mechanism numerically counting down the number of actuations

NOTE The actuation counter may either be an accessory or integrated with the ADDD.

3.5
ADDD system
integrated system comprised of the ADDD, patient interface and the medication (i.e. a combination product)

3.6
aerosol
suspension of particles in gas

[ISO 27427:2009, definition 3.1]

NOTE 1 Particles can be liquid and/or solid.

NOTE 2 The gas can be the driving gas or ambient air.

3.7
aerosol drug delivery device
ADDD
device for the delivery of medication in the form of an aerosol

3.8
claimed lifetime
time period, and/or number of actuations, stated by the ADDD manufacturer within which the device functionality profile of the ADDD will remain within the design specification comprising the timeframe within which the patient uses the ADDD

NOTE Claimed lifetime is not necessarily the same as the shelf life of the ADDD.

3.9
claimed lifetime testing
performance evaluation simulating the claimed lifetime stated by the ADDD manufacturer within which the device functionality profile of the ADDD will remain within the design specification

3.10
combination product
ADDD used with a specific medication

3.11
content indicator
visual indicator showing the amount of medication remaining in the ADDD

NOTE A content indicator can be either an accessory or integrated with the ADDD.

3.12
design verification
confirmation by examination and provision of objective evidence that specified design requirements have been fulfilled

3.13
device functionality profile
DFP
parameters and tolerance intervals used to assess whether the ADDD meets the manufacturer's design specification

NOTE It must be possible to evaluate the properties using laboratory (*in vitro*) testing.

3.14
dose
mass of API prescribed to elicit a therapeutic response

NOTE 1 More than one actuation of the ADDD may be required to achieve the specified dose.

NOTE 2 For certain APIs, mass can be replaced by the use of biological equivalent units.

3.15
emitted mass
EM
mass of medication per actuation emitted from the ADDD mouthpiece at the patient interface

3.16
excipient
any substance included with the active pharmaceutical ingredient(s) of the medication

3.17
fixed-dose ADDD
ADDD where the amount of medication delivered per actuation (mass or bioequivalent units), either pre-metered or from a reservoir, is pre-set by the manufacturer

3.18
hand-held
capable of being held in the hand and moved to the patient's mouth or nose for use

3.19
harm
physical injury or damage to the health of people, or damage to property or the environment

[ISO 14971:2007, definition 2.2]

3.20
holding chamber
accessory comprising a volume between the ADDD and the patient's mouth or nose and designed to contain the aerosol following an actuation

NOTE A holding chamber has some means for retaining the aerosol after ADDD actuation has occurred and prior to the patient inhaling.

3.21
instructions for use
directions provided by the manufacturer for the correct handling and operation of the ADDD

3.22
integral supply of medication
manufacturer-sealed supply of medication contained by or provided to an ADDD

EXAMPLE Reservoirs or blisters.

3.23
intended use
application of the ADDD that is specified by the manufacturer in the instructions for use

3.24
in-use life
time specified by the manufacturer that the medicinal product can be used after opening or after first use by the patient

3.25
label
text (printed or graphic) affixed to or present (etched) on or accompanying the ADDD

3.26
label claim
amount of API (mass) marked on the label of the ADDD

NOTE In some countries the label claim is the amount of API that is emitted from the ADDD mouthpiece. In other countries the label claim might be the amount of API that is metered by the ADDD, but not necessarily all emitted from the mouthpiece of the ADDD.

3.27
medication
API(s) alone or API(s) formulated with excipients(s)

3.28
medicinal product
the medication in the ADDD

3.29
nasal delivery
administration of medication to or through the nose

3.30
nominal flow rate
volumetric air flow rate through the ADDD which is described by the manufacturer as typical for the intended patient population

3.31
operator
person (patient/user) using the ADDD

3.32
oral delivery
administration of medication to or through the mouth

3.33
placebo
dosage form that does not contain API

3.34
pre-filled
ADDD in which the medication is inserted at manufacture and cannot be replenished by the patient

3.35
pre-metered
defined amount of medication equal to one actuation placed during its manufacture into a package (blister, capsule) for use in the ADDD

3.36
primary packaging container
the container in which the medication is enclosed

3.37
refillable ADDD
designed to be replenished with medication for further operation

3.38
respiratory tract
anatomical region comprising nasal, oral, pharyngeal, tracheal, bronchial and alveolar regions

3.39
risk
combination of the probability of occurrence of harm and the severity of that harm

[ISO 14971:2007, definition 2.16]

3.40
risk assessment
RA
overall process comprising a risk analysis (estimation) and a risk evaluation

[ISO 14971:2007, definition 2.18]

3.41
secondary packaging
container in which the ADDD is enclosed

3.42
selected-dose ADDD
device where the amount of medication delivered per actuation (mass or bioequivalent units), either pre-metered or from a reservoir, is set by the operator

3.43
size distribution
relationship between weighting (by number, surface area, volume or mass) and size that describes the population of aerosol particles or droplets

3.44
spacer
accessory that increases the distance between the ADDD and the patient's mouth or nose

3.45
system verification test
test of the ADDD system conducted after successfully satisfying the device functionality profile

3.46
visible defects
observable imperfections that prevent the ADDD either from meeting its device functionality profile or from being safe to use

4 Symbols and abbreviated terms

P_T For a given ADDD device functionality profile, the parameter of interest (e.g. flow path resistance) and the target value (per the design specification) being evaluated.

k Tolerance limit factor – determined from the confidence level, probability content, p, and the number of measurements, n, conducted for each P_T.

p Probability content.

n Number of ADDDs required for a given test.

$\bar{x}$ The sample average – based on a random sample, an estimate of the population average:

$$\bar{x} = \Sigma P_{meas}/n.$$

USL Upper specification limit for a given P_T.

LSL Lower specification limit for a given P_T.

RH Water vapour pressure at a particular temperature expressed as a percentage of the saturation vapour pressure at the same temperature.

5 Requirements

5.1 General

Unless justified by the risk assessment, the following general requirements apply.

a) The ADDD shall be designed so that, when operated in accordance with the instructions for use, it provides the emitted mass or dose as specified and verified by the ADDD manufacturer (see 5.4).

b) The ADDD shall be designed so that the operator is aware that the ADDD has been actuated.

c) The ADDD shall be designed to minimize the risk of inadvertent actuation.

d) The performance of the combination of the ADDD and any accessory specified by the ADDD manufacturer shall comply with the device functionality profile and system verification test applicable to that combination. The manufacturer shall identify as part of the ADDD or ADDD system the specific accessories that are suitable for use.

e) The ADDD shall be designed so that the operator can determine when the medication intended to be delivered is near completion and is near or has reached exhaustion.

f) A prefilled ADDD with an actuation counter or content indicator shall not reset once the end of life is reached. A refillable ADDD with an integrated counter shall allow for resetting once the ADDD is replenished with medication.

g) The manufacturer shall provide information to the operator to indicate when the ADDD needs to be replaced or has reached the end of its in-use life (see Annex A for rationale). This requirement also applies to all accessories necessary to meet the device functionality profile requirements.

h) The design process shall include a provision of rationale for the selection of materials. In the selection of materials to be used in device manufacture, the first consideration should be fitness for purpose with regard to characteristics and properties, including chemical, toxicological, physical, electrical, morphological and mechanical attributes of the material.

To give assurance that the final product will perform as intended and be safe for human use, the programme shall include an appropriate biological evaluation in accordance with ISO 10993-1.

NOTE 1 ISO 10993-1 gives guidance on which parts of the ISO 10993 series are relevant to comply with.

i) The ADDDs shall be designed to minimize:

— ingress of foreign particles;

— creation of particles from the ADDD itself (e.g. abrasion);

— microbiological contamination.

j) ADDDs and/or their components which by their design or intended purpose are required to be sterile, shall be designed so that they can be subjected to sterilization processes in accordance with ISO 17665-1, ISO 11135-1 or ISO 11137 or other validated sterilization process.

k) Software shall be designed based on a life cycle model in accordance with IEC 62304. The ADDD shall fulfil the applicable requirements of IEC 62304.

l) ADDDs and/or their components, which by their design or intended purpose are required to be cleaned, disinfected or sterilized by the operator, shall be provided with adequate instructions for the operator to perform the cleaning, disinfection or sterilization. These methods shall be verified by the manufacturer as achieving their intended purpose.

m) ADDDs with electrical components shall comply with IEC 60601-1, IEC 60601-1-2 and IEC 62366.

n) If the ADDD contains an electronic alarm system, the ADDD shall comply with IEC 60601-1-8 and IEC 62366.

o) For pre-filled and fixed-dose ADDDs the dose and number of actuations shall be clearly indicated on the ADDD.

NOTE 2 This could be accomplished by labelling.

p) In the case of selected-dose ADDDs, the following shall be clearly indicated (see Annex A for rationale):

— the magnitude and units (e.g. μg, ml, IU etc) for the selected dose;

— that the selected dose is ready to be delivered.

q) A selected-dose ADDD (see Annex A for rationale) shall be designed so that one of the following applies:

— a dose cannot be set to a value greater than the medication that remains;

— the ADDD does not allow delivery if the dose set is greater than the medication that remains;

— the ADDD indicates the amount of medication delivered (i.e. portion of the set dose delivered);

— the ADDD indicates the amount of medication NOT delivered (i.e. portion of the set dose yet to be delivered).

r) The ADDD shall be designed such that the identity of the medication in pre-filled devices can be determined by the operator or that medication to be used with non-pre-filled ADDDs is clearly specified.

NOTE 3 This could be accomplished by labelling.

5.2 Risk assessment requirements

The manufacturer shall conduct a risk assessment, in accordance with ISO 14971, that will determine the parameters that shall then be included in the device functionality profile. The risk assessment shall also determine the appropriate statistical requirements for the system verification test. That risk assessment shall consider, at a minimum, all aspects of the intended use of the ADDD, as listed in ISO 14971:2007, Annex C.

5.3 Device functionality profile

There shall be established a device functionality profile (DFP) based on the outcome of the risk assessment in 5.2. The DFP shall consist of identified critical functions and design features, test methodology, tolerance limits and acceptance criteria (see Annex B).

5.4 System verification test

Once the DFP has been completed (and has been provided with acceptance criteria), a system verification test shall be performed on the ADDD. This comprises either emitted mass or dose testing, as determined from the risk assessment. This ADDD system verification test shall only be performed at standard atmosphere and

a nominal flow rate with either the placebo, the medication or a representative medication. If the ADDD is designed to operate over a range of dose sizes, the low, mid and high dose size shall be evaluated (see C.2).

5.5 Uncertainty of measurements and conformance with specification

Due to the nature of the statistical tolerance interval approach (6.4.2), random measurement error is automatically included in the standard deviation and a large measurement uncertainty will make it harder to pass the test.

Systematic measurement uncertainty (e.g. bias due to calibration error, instrumentation or other day-to-day variation) is not automatically included in the test and shall be considered when setting the parameter specifications and tolerances.

5.6 Test requirements

5.6.1 General

ADDDs that have different operating temperatures and/or environmental requirements different from those specified in this International Standard shall be subjected to the relevant test at those acceptable operating conditions. These acceptable conditions shall be stated in the instructions for use.

5.6.2 ADDDs subjected to standard, cool and hot atmospheres and after claimed lifetime testing

When tested in accordance with to 6.2.2:

— none of the ADDDs shall have visible defects after being subjected to standard, cool and hot atmospheres;

— the ADDDs shall have a device functionality profile within the limits specified by the manufacturer after being subjected to standard, cool and hot atmospheres;

— none of the ADDDs shall have visible defects after being subjected to claimed lifetime testing;

— the ADDDs shall have a device functionality profile within the limits specified by the manufacturer after being subjected to claimed lifetime testing.

ADDDs designed for a single actuation shall be excluded from claimed lifetime testing.

5.6.3 ADDDS subjected to heat storage atmosphere

When tested in accordance with 6.2.3:

— none of the ADDDs shall have visible defects after being subjected to a heat storage atmosphere;

— the ADDDs shall have a device functionality profile within the limits specified by the manufacturer after being subjected to a heat storage atmosphere.

5.6.4 ADDDs subjected to cold storage atmosphere

When tested in accordance with 6.2.4:

— none of the ADDDs shall have visible defects after being subjected to a cold storage atmosphere;

— the ADDDs shall have a device functionality profile within the limits specified by the manufacturer after being subjected to a cold storage atmosphere.