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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.

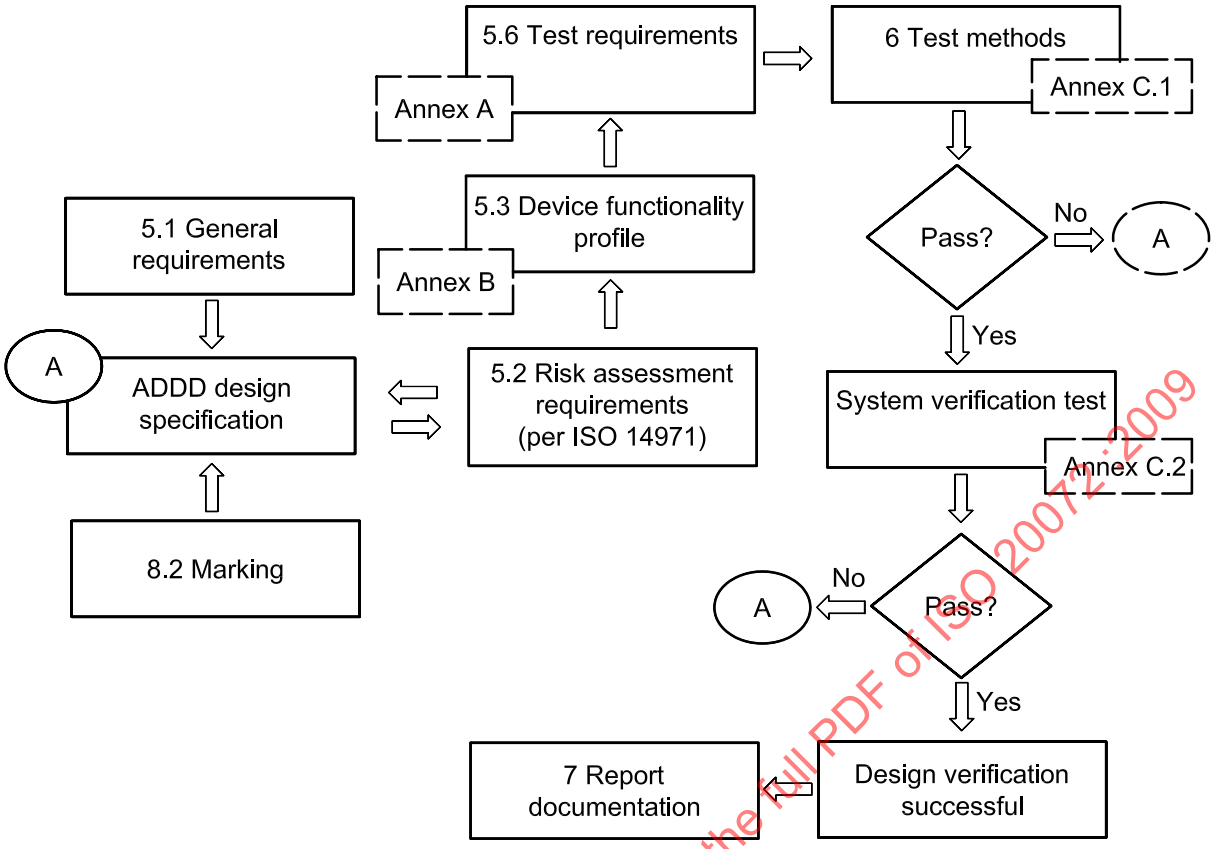

Figure 1 — ADDD design verification process

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.

5.6.5 ADDDs subjected to cyclical atmosphere

When tested in accordance with 6.2.5:

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

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

5.6.6 ADDDs subjected to free fall

When tested in accordance with 6.2.6:

— none of the ADDDs shall have visible defects after being subjected to free fall;

— the ADDDs shall have a device functionality profile within the limits specified by the manufacturer after being subjected to free fall.

If, per the risk assessment, the conditions specified in 5.6 are not justified and more appropriate “worst-case” conditions are identified, test the ADDD according to these new conditions and document in the test report.

5.6.7 ADDDs subjected to vibration and shock

When tested in accordance with 6.2.7:

— none of the ADDDs shall have visible defects after being subjected to vibration and shock;

— the ADDDs shall have a device functionality profile within the limits specified by the manufacturer after being subjected to vibration and shock.

If, per the risk assessment, the conditions specified in 5.6 are not justified and more appropriate “worst-case” conditions are identified, the ADDD shall be tested according to these new conditions and document in the test report.

5.6.8 ADDDs with electrical components subjected to electromagnetic compatibility (EMC)

5.6.8.1 General

The requirements given in 5.6.8.2 and 5.6.8.3 are requirements substituting those specified in IEC 60601-1-2 as the latter standard covers requirements for electro-medical appliances in general only, and it does not specifically address ADDDs.

ADDDs without electrical components shall not be required to fulfil the requirements of this sub-clause.

If, per the risk assessment, the conditions specified in 5.6 are not justified and more appropriate “worst-case” conditions are identified, the ADDD shall be tested according to these new conditions and document in the test report.

NOTE The tests specified in 5.6.8.2 and 5.6.8.3 are based on the requirements given in the collateral standard IEC 60601-1-2. In that standard, EMC references are given to IEC 61000-4-1 and IEC 61000-4-2, Edition 2.1 and IEC 61000-4-3, Edition 3.

5.6.8.2 Electrostatic discharge

When tested in accordance with 6.2.8:

— none of the ADDDs shall have visible defects after being subjected to electrostatic discharge levels;

— the ADDDs shall have a device functionality profile within the limits specified by the manufacturer after being subjected to electrostatic discharge levels.

5.6.8.3 Radio frequency (RF) fields

When tested in accordance with 6.2.8:

— none of the ADDDs shall exhibit erroneous indications during the radio frequency sweep;

— none of the ADDDs shall have visible defects after being subjected to radio frequency fields;

— the ADDDs shall have a device functionality profile within the limits specified by the manufacturer after being subjected to radio frequency fields.

5.6.9 ADDDs subjected to sterilization

When tested in accordance with 6.2.9:

— none of the ADDDs shall have visible defects after being subjected to sterilization;

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

ADDDs that do not require sterilization shall not be required to fulfil the requirements of this sub-clause.

5.6.10 ADDDs subjected to cleaning and disinfection

When tested in accordance with 6.2.10:

— none of the ADDDs shall have visible defects after being subjected to cleaning and disinfection;

— the ADDDs shall have a device functionality profile within the limits specified by the manufacturer after being subjected to cleaning and disinfection.

The cleaning process specified in the instructions for use shall not have an adverse effect on the device functionality profile of the device.

ADDDs that do not require cleaning and disinfection shall not be required to fulfil the requirements of this sub-clause.

5.6.11 ADDDs subjected to system verification test

— none of the ADDDs shall have visible defects after being subjected to a system verification test;

— the ADDDs shall have an emitted mass or dose within the limits specified by the manufacturer after being subjected to a system verification test (see C.2 for guidance regarding the appropriate methods to evaluate aerosol measurements).

6 Test methods

6.1 General

To ensure that both inter-device and intra-device variability are adequately assessed, each ADDD shall provide only one data-set for each DFP parameter, P_T, being evaluated and for the system verification test.

For refillable ADDDs to satisfy test requirements defined in Clause 5, it is not necessary to perform test evaluations (device functionality profile and visual inspection) after each test procedure specified in 6.2.2 to 6.2.11. In such cases, the test evaluations shall be performed after the last test to which the ADDD has been subjected.

NOTE If this final evaluation produces a failure, the manufacturer might be unable to determine at which point in the testing series the failure occurred.

Unless otherwise specified, all tests and test evaluations shall be performed at standard atmosphere conditions (as defined in 6.3.2).

The ADDD shall be prepared in accordance with the instructions for use.

The ADDD shall be operated either manually or automatically, in a way that simulates operation by the end-user, as described in the instructions for use.

6.2 Test procedures

6.2.1 General

The purpose of these tests is to evaluate the ADDD device function when operated at the specified environmental conditions. For this reason testing should be performed at that environmental condition. However, where justified in order to be equivalent to the risk assessment (e.g. the time required to remove ADDD from the pre-conditioning environment and test is sufficiently short as to not impact the intent of the given requirement), testing may be performed at ambient environmental conditions.

Using the probability content levels shown in Table 1, the two-sided statistical tolerance interval (or one-sided statistical tolerance interval, as appropriate) for a given test (see 6.4.2) and P_T can be calculated.

The manufacturer shall select the appropriate number of ADDDs to test for the tests specified in 6.2.2 to 6.2.11 (denoted by n), recognizing that the target k value will increase as the sample size selected decreases.

The minimum test requirements to be evaluated are summarized in Table 2. If, per the risk analysis, flow rate has an effect on the parameter being tested, then that test shall be conducted at the upper and lower boundaries of the design specification flow rate range. Otherwise, the nominal flow rate shall be used.

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

Subject n new ADDDs to the standard atmosphere specified in 6.3.2 and evaluate the device functionality profile at these conditions in accordance with 6.4.2.

Subject the same ADDDs to the cool atmosphere specified in 6.3.3 and evaluate the device functionality profile at these conditions in accordance with 6.4.2.

Subject the same ADDDs to the hot atmosphere specified in 6.3.4 and evaluate the device functionality profile at these conditions in accordance with 6.4.2.

Determine the claimed lifetime of the ADDD.

Subject n ADDDs tested above to the claimed lifetime testing (simulate manual use in accordance with the instructions for use) until 1,5 × the number of actuations of the claimed lifetime (in accordance with the manufacturer's product file) is reached.

If the ADDD is designed to stop working after a limited time or number of actuations (e.g. pre-filled multi-dose ADDD, refillable ADDD with non-replaceable batteries), the total number of actuations (less the number of actuations required for evaluation of the device functionality profile) shall be adopted for this test.

Visually inspect the ADDDs in accordance with 6.4.4.

Subject the same ADDDs above to the standard atmosphere specified in 6.3.2 and evaluate the device functionality profile in accordance with 6.4.2.

Table 1 — Minimum confidence and probability content requirements for data by test type

Test type (and minimum confidence)	**Test type** (and minimum probability content, p)	**Examples of n, number of ADDDs to test** [a]	**Corresponding two-sided target k for each n** (from Annex D)	**Corresponding one-sided target k for each n** (calculated per ISO 16269-6)
DFP (with the exception of aerosol measurements) [b] In-use condition testing 0,95	In-use condition testing ($p = 0{,}975$)	60 30 25 20 15	2,670 2,921 3,015 3,154 3,386	2,384 2,609 2,691 2,810 3,005
DFP (with the exception of aerosol measurements) Extreme condition testing 0,95	Extreme condition testing ($p = 0{,}950$)	60 30 25 20 15	2,335 2,555 2,638 2,760 2,965	2,023 2,220 2,292 2,397 2,567
System verification test and DFP (aerosol measurements only) [b]	As determined by the risk assessment	As determined by the risk assessment	NA	NA

NOTE The sampling plans for inspection selected for this International Standard are intended to verify the design at a high confidence level. The sampling plan does 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.

[a] The numbers of ADDDs, n, in Table 1, are provided for example only.

[b] Aerosol measurements are those measuring the dose, emitted mass or any particle size measurements of the aerosol that is emitted.

Table 2 — Minimum DFP test requirements (with the exception of aerosol measurements [a])

Test type	**Confidence**	**Content P**	**Sub-clause**	**Descriptions**	**Refillable ADDD**	**Pre-filled ADDD**
In-use condition testing	0,95	($p = 0{,}975$)	5.6.2 5.6.3 5.6.4 5.6.4	Standard, cool, hot, lifetime, heat storage, cold storage	X X X X	X X X X
Extreme condition testing	0,95	($p = 0{,}950$)	5.6.5 5.6.6 5.6.7 5.6.8 [c] 5.6.8 [c] 5.6.9 [d] 5.6.10 [e]	Cyclical [b] free fall vibration, shock electrostatic RF fields sterilization cleaning	X X X X X X X	– X X X X X X

NOTE "X" signifies a requirement and "–" signifies an exemption from the requirement.

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

[b] Prefilled ADDDs shall be exempt from cyclical atmosphere testing.

[c] ADDDs without electronic components shall be exempt from electromagnetic compatibility testing.

[d] ADDDs that do not require sterilization shall be exempt from sterilization testing.

[e] ADDDs that do not require cleaning and disinfection shall be exempt from cleaning and disinfection testing.

6.2.3 ADDDs subjected to heat storage atmosphere

Subject n new ADDDs to the heat storage atmosphere specified in 6.3.5.

Visually inspect the ADDDs in accordance with 6.4.4.

Subject the ADDDs to the standard atmosphere specified in 6.3.2.

Evaluate the device functionality profile in accordance with 6.4.2.

6.2.4 ADDDs subjected to cold storage atmosphere

Subject n new ADDDs to the cold storage atmosphere specified in 6.3.6.

Visually inspect the ADDDs in accordance with 6.4.4.

Subject the ADDDs to the standard atmosphere specified in 6.3.2.

Evaluate the device functionality profile in accordance with 6.4.2.

6.2.5 ADDDs subjected to cyclical atmosphere

Subject n new ADDDs to the cyclical atmosphere specified in 6.3.7.

Visually inspect the ADDDs in accordance with 6.4.4.

Subject the ADDDs to the standard atmosphere specified in 6.3.2.

Evaluate the device functionality profile in accordance with 6.4.4.

6.2.6 ADDDs subjected to free fall

Prepare the ADDD by removing from the carton and remove any other secondary packaging. Perform the test:

a) with the cap (e.g. mouthpiece cover) in position;

b) with the cap removed.

The free fall test shall be performed using a free fall system as specified in IEC 60068-2-32, or other justified worst case conditions.

The test surface shall be smooth, hard, rigid and made of steel of 3 mm thickness backed by wood of between 10 mm and 19 mm thickness.

Subject n new ADDDs to the standard atmosphere specified in 6.3.2 and continue as described below.

Drop each ADDD three times by free fall in accordance with the conditions specified in IEC 60721-3-7 Class 7M3, on to the test surface, in a minimum of three substantially differing orientations, derived from the typical orientations for storage and use in consideration of the risk analysis and device development history. The ADDD shall be dropped in a non-turbulent way.

Visually inspect the ADDDs in accordance with 6.4.4.

Evaluate the device functionality profile in accordance with 6.4.2.

6.2.7 ADDDs subjected to vibration and shock

Prepare the ADDDs according to the instructions for use.

Subject n new ADDDs to the standard atmosphere specified in 6.3.2 and continue as described below.

Subject the ADDDs to vibration in accordance with the methods, procedures and equipment described in IEC 60068-2-64, or other justified worst case conditions.

Subject the ADDDs to the conditions specified in IEC 60721-3-7 Class 7M3.

The vibration time in each direction shall be 1 h.

Subject the ADDDs to the shock test in accordance with IEC 60068-2-27.

Subject the ADDDs to the conditions specified in IEC 60721-3-7 Class 7M3.

Visually inspect the ADDDs in accordance with 6.4.4.

Evaluate the device functionality profile in accordance with 6.4.2.

ADDDs that cannot satisfy the requirements of vibration and shock testing in this International Standard shall be subjected to such testing at the acceptable conditions. Appropriate guidance as to the avoidance of excessive vibration shall be included in the instructions for use.

For intensive transportation of equipment over heavy surfaces, the Type I shock test should be over a number of 100 shocks positive and 100 negative.

NOTE 1 IEC 60068-2-64 describes the test equipment for the vibration test.

NOTE 2 For clarification: the test described above is applicable to electrical and non-electrical ADDDs (there are no other shock standards available for non-electrical ADDDs).

— IEC 60721-3-7 specifies requirements for portable ADDDs. Class 7M3 is selected because of its description of transportation of the ADDD;

— IEC 60068-2-27 describes the test equipment for the shock test;

— the shock response test Type I represents transport of the ADDD in its packaging;

— the shock response test Type II represents the ADDD in use (without packaging).

6.2.8 ADDDs with electrical components subjected to electromagnetic compatibility (EMC) testing

Subject n new ADDDs to the standard atmosphere specified in 6.3.2 and continue as described below.

Test the ADDDs for exposure to electrostatic discharge and radio frequency (RF) as follows.

Place n ADDDs with the primary packaging on a metal reference plane as specified in IEC 61000-4-2, or other justified worst case conditions.

Apply contact discharges of (± 2, ± 4 and ± 8) kV to conductive accessible parts and coupling planes.

Apply air discharges of (± 8, ± 10, ± 12 and ±1 5) kV to non-conductive accessible parts.

The number of discharges at each level and polarity shall be 10 with a time interval of 1 s between the individual discharges.

Test the same ADDDs in accordance with IEC 61000-4-3 [transversal electromagnetic mode (TEM) cells or gigahertz transverse electromagnetic (GTEM) cells may be used as described in Annex D of that standard].

As stated in IEC 61000-4-3, the requirement for field uniformity shall be fulfilled in the area corresponding to the unit under test.

Test the same ADDDs at the 10 V/m level (unmodulated carrier) in the frequency range of (26 to 2 000) MHz.

The test signal shall be AM modulated with 1 kHz sinusoidal and to a modulation depth of 80 %.

Perform the test in each of the three axes of the ADDD.

Visually inspect the ADDDs in accordance with 6.4.4.

Evaluate the device functionality profile in accordance with 6.4.2.

6.2.9 ADDDs subjected to sterilization

Subject n new ADDDs to the specified sterilization procedure described in the product labelling.

Visually inspect the ADDDs in accordance with 6.4.4.

Subject the ADDDs to the standard atmosphere specified in 6.3.2.

Evaluate the device functionality profile in accordance with 6.4.2.

6.2.10 ADDDs subjected to cleaning and disinfection

Subject n new ADDDs to the specified cleaning and disinfection procedure described in the instructions for use.

Visually inspect the ADDDs in accordance with 6.4.4.

Subject the ADDDs to the standard atmosphere specified in 6.3.2.

Evaluate the device functionality profile in accordance with 6.4.2.

6.2.11 ADDDs subjected to system verification test

Subject n new ADDDs to the standard atmosphere specified in 6.3.2.

Evaluate the emitted mass or dose in a manner consistent with the instructions for use.

See Annex C.2 for guidance regarding the appropriate methods to evaluate aerosol measurements.

6.3 Test conditions

6.3.1 General

Unless otherwise specified, test measurements shall be performed at standard atmospheric conditions as specified in 6.3.2. A rationale for the environmental and mechanical conditions described herein can be found in C.1.

6.3.2 Standard atmosphere

Standard atmospheric conditions shall be defined as:

— temperature: (25 ± 2) °C;

— relative humidity: (60 ± 5) % RH.

The ADDDs are subjected to storage for at least 4 h in this atmosphere.

6.3.3 Cool atmosphere

The ADDDs are placed in a test chamber for at least 4 h in the following cool atmosphere:

— temperature: (5 ± 3) °C;

— relative humidity: ambient RH.

6.3.4 Hot atmosphere

The ADDDs are placed in a test chamber for at least 4 h in the following hot atmosphere:

— temperature: (40 ± 2) °C/(75 ± 5) % according to ICH;

— relative humidity: not more than 25 % RH.

6.3.5 Heat storage atmosphere

The ADDDs are placed in a test chamber for at least 96 h in the following dry heat atmosphere:

— temperature: (50 ± 2) °C;

— relative humidity: ambient RH.

6.3.6 Cold storage atmosphere

The ADDDs are placed in a test chamber for at least 96 h in the following cold atmosphere:

— temperature: (–20 ± 5) °C.

6.3.7 Cyclical atmosphere

The ADDDs are placed in a test chamber. Conditioning in accordance with IEC 60068-2-30 is carried out as follows:

— variant 1 (see IEC 60068-2-30:2005, Figure 2a);

— upper temperature: (55 ± 2) °C;

— 6 cycles.

NOTE The relevant clauses of IEC 60068-2-30:2005 are: Clause 4: Testing chamber, Clause 7: Conditioning and Clause 9: Recovery.

6.4 Test evaluations

6.4.1 Test substance

For aerosol measurements, the substance to be tested in evaluating the device functionality profile (if required by the risk assessment) and the system verification test shall be either the medication, a representative medication or a placebo that has appropriate physical and chemical properties representative of the medication that will be used in the marketed ADDD. If a representative medication or placebo for the medication is used, it shall be supported by the risk assessment and may require bridging studies to demonstrate suitability.

6.4.2 Device functionality profile

With the exception of aerosol measurements, the device functionality profile shall be evaluated by selecting and testing a number of ADDDs. Assuming that the test results are normally distributed and that each measurement is independent, the following method enables test results to be used as the basis for determining a statistical tolerance interval for the relevant dose selections, i.e. an interval such that there is a fixed probability (confidence level) that the interval will contain at least a proportion (p, probability content) of the true population from which the sample is taken. The statistical tolerance interval is two-sided, and the limits of the interval are called "statistical tolerance limits" or "natural limits of the process". To pass the device functionality profile requirement, there shall be a 95 % confidence that at least p of all values will fall between the previously determined tolerance limits (also referred to as the upper and lower specification limits) for the relevant P_T.

The two-sided statistical tolerance interval is calculated using the average, $\bar{x}$, plus or minus the standard deviation, s, multiplied by a tolerance limit factor, k:

$$\bar{x} \pm k \times s$$

where $\bar{x}$ is the average of the sample values.

The factor, k, is determined based upon the confidence level (95 %), probability content, p, and the number of measurements, n, taken for a given P_T. Annex D contains a comprehensive table of two-sided tolerance limit factors for the 95 % confidence level.

An ADDD population satisfies the requirements when, for a given P_T, the following expressions are fulfilled:

$$\bar{x} + (k \times s) \leqslant \text{USL};$$

$$\bar{x} - (k \times s) \geqslant \text{LSL}.$$

NOTE 1 Using ISO 16269-6, a similar set of relationships can be applied for one-sided statistical tolerance intervals. It also addresses situations when the data is not normally distributed. ISO 16269-6:2005, Annex E, lists the tolerance limit factors for the construction of two-sided statistical tolerance intervals when the true population mean and standard deviation are not known.

NOTE 2 For aerosol measurements identified as part of the DFP, refer to C.2.

NOTE 3 The above acceptance criterion is simple to evaluate. A more elaborate and precise acceptance criterion is provided in Annex E. Either of the criteria may be used in the performance evaluation.

6.4.3 System verification test

While no specific methodology is defined as part of this International Standard, C.2 provides some perspective and guidance relative to evaluating the emitted mass or dose.

6.4.4 Visual inspection

Evaluate and confirm the functional performance (e.g. stored data, settings, dose or indications) of each ADDD that has electronic components.

Markings on each ADDD (e.g. words, characters, numbers, symbols, quantity/volume scales, grid lines, and index marks) shall remain visible and easily legible by normal vision, or vision corrected to normal, at environmental lighting conditions of 215 (± 20) lx.

Inspect each ADDD for significant defects under normal (corrected, if needed) vision. Defects in electronic parts leading to non-functioning are permitted if the non-functioning is obvious to the operator.

The inspection shall in particular include checking for significant defects such as:

— displaced parts;

— markings no longer in place, visible and clearly legible by normal vision;

— cracks in the body and/or component of the ADDD that might impact the safe functioning of the ADDD;

— compromised assembly bonds, joints and alignments.

7 Test report

The test report shall be maintained in accordance with records needed to provide evidence that the realization processes and resulting ADDD meet the requirements. A summary of results from testing in accordance with Table 1 shall be described in the report.

8 Information supplied by the manufacturer

8.1 General

The ADDD shall be accompanied by instructions for use, taking into account the training and knowledge of the operators. Instructions for use shall be included in/on the secondary packaging container.

8.2 Marking

8.2.1 Marking on the ADDD

Any marking on the ADDD that is essential for the identification and safe use of the device shall be legible and indelible after being subjected to the test requirements specified in 5.6. Legibility shall be assessed using normal or corrected-to-normal vision at an environmental lighting condition of (215 ± 20) lx.

The marking on the ADDD shall contain at least the following:

a) the product manufacturer;

NOTE A trademark or logo can be sufficient to identify the manufacturer.

b) the product name;

c) the lot number or the serial number;

d) if the ADDD contains an integral supply of medication, information on the medication delivered, the label claim, the labelled number of actuations and the expiry date in the format expressing at least year and month (e.g. 2008-12);

e) if the ADDD or any component is provided sterile, a statement or symbol, in accordance with ISO 15223-1, indicating the method of sterilization.

The manufacturer shall mark accessories so that they are clearly identified. The marking on accessories shall contain at least a), b) and c).

8.2.2 Marking on the secondary packaging container

Any marking on the secondary packaging container that is essential for the safe use of the ADDD shall be legible. Legibility shall be assessed using normal or corrected-to-normal vision at an environmental lighting condition of (215 ± 20) lx.

The marking on the secondary packaging container shall contain at least the following:

a) the product manufacturer;

b) the product name;

c) the content of the primary packaging container;

d) whether the ADDD contains an integral supply of medication or whether the primary packaging container of the ADDD contains a supply of medication, information on the medication delivered, the label claim, the labelled number of actuations and the expiry date in the format expressing at least year and month (e.g. 2008-12);

e) the lot number or the serial number; on ADDDs not having an integral supply of medication, this requirement is determined by the risk assessment;

f) any special storage and/or handling conditions.

8.3 Instructions for use

The instructions for use shall contain at least the following information:

a) the information required in 8.2.1 except that the information regarding expiry date, lot number or serial number can be omitted;

b) if no expiry date is specified for a refillable ADDD, the instructions shall indicate for how long after first use or for how many actuations it is intended to be used before being discarded;

c) information on how the ADDD is to be correctly used, using graphics when appropriate:

   1) how it should be removed from the package, if this is relevant;

   2) any preparatory actions for first-time use (e.g. battery loading, function testing) or instructions for assembly or for use with an accessory, as appropriate;

   3) in the case of an ADDD that does not contain an integral supply of medication, how it is assembled and/or loaded with a dose of medication;

   4) appropriate actions that need to be performed prior to actuation (e.g. shaking, priming, device orientation, selecting the dose, etc.);

   5) instructions on how the operator is to actuate and to inhale (e.g. exhalation, actuation, inspiratory effort, duration, breath holding, repetition of inhalation);

   6) instructions on how the operator is to prepare the ADDD for storage or non-use after actuation;

   7) instructions on how the ADDD is to be re-used, cleaned, disinfected or sterilized as appropriate, if it is refillable;

   8) instructions on how to dispose of the ADDD or parts thereof at the end of their intended life;

d) information on warnings or precautions to be taken:

   1) a statement that if it appears to the operator that the ADDD is not functioning correctly, to seek advice from a healthcare professional;

   2) how the operator can synchronize inspiratory effort with actuation, if this is needed;

   3) in the case of a selected-dose ADDD, that it shall only be used by operators able to select the correct dose;

   4) in the case of a selected-dose ADDD, how the ADDD operates when the amount of medication available is less than the dose the operator intends to select;

e) in the case of a selected-dose ADDD, instructions on the dose-setting method and the dose-setting range;

f) if acceptable storage temperatures are other than those specified in 6.3 (+40 °C and −20 °C) the acceptable temperature range for storage of the ADDD without medication;

g) any special storage requirements;

h) type of replaceable batteries and their number, if used, and instructions to recycle the used batteries;

i) a description of any special features;

j) details advising the operator on any contra-indications and any precautions to be taken, as appropriate; these details should cover precautions to be taken in the event of breakage or changes in the performance of the ADDD;

k) identification of accessories that are suitable for use, where known.

Annex A
(informative)

Rationale for requirements

A.1 Introduction

This annex contains rationale statements for some of the requirements of this International Standard. It is included to provide additional insight into the reasoning that led to the requirements and recommendations that have been incorporated in this International Standard. It is considered that knowledge of the reasons for the requirements will not only facilitate the proper application of this International Standard, but will expedite any subsequent revisions.

The scope of this International Standard covers a diversity of ADDDs according to their design, construction and operation: passive *versus* active devices, devices containing a supply of medication *versus* unit doses, refillable *versus* non-refillable, fixed dose *versus* selected dose, etc.

The requirements of this International Standard were developed taking into account currently marketed ADDDs as well as ADDDs that are still under development at the time of writing. As the technology is rapidly evolving, this International Standard hopes to bridge the old and the new, without hindering the former or restricting progress in the latter. Consequently, this informative annex is provided to allow the reader to understand the thinking of the authors.

The committee is aware that certain currently marketed devices are not able to meet some of the requirements. However, since this document is designed to encourage future development and progress, the committee believes Clause 5 contains requirements that will advance patient safety.

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

The numbering of the following rationale corresponds to the numbering of the clauses in the main text. The numbering is, therefore, not consecutive.

A.2 Rationale for requirements (5.1)

5.1 a): Concerning the delivery of the emitted mass, the objective for new ADDDs should be to ensure that an actuation has occurred from the ADDD. If the patient is not able to verify this, then the design of new ADDDs should ensure that objective by providing indicative means with the device.

5.1 b): This subclause concerns the awareness of the patient that the ADDD has been actuated. Feedback that actuation has occurred should provide positive confirmation to the operator and not just rely on the correct use of the device according to the instructions.

5.1 g): The information concerning the number of actuations or amount of medication left inside the device is essential for all ADDDs where that amount of medication is not immediately visible or measurable by the operator.

For ADDDs that can be refilled and thus re-used, the focus is on establishing how many times or for how long the ADDD can be used before being replaced.

5.1 i): This requirement is intended to prevent foreign materials entering the aerosol transport pathway of the ADDD or interfering with the mechanism that would prevent usual function of the ADDD, and prevent inhalation of foreign material (discrete objects that are not part of the ADDD or its medication).

5.1 p): This subclause only applies to ADDDs that have, or allow input from, a reservoir that contains a labelled volume of medication from which the operator can select a dose.

The device must be able to indicate the magnitude and unit of the dose the operator can select. These units must be the same as the units in which the medicine is labelled.

For example, an insulin medication ADDD which has a reservoir (fixed or replaceable) which contains 100 IU of insulin when full, must display both the magnitude and units (e.g. 50 IU) that the operator has selected.

A morphine medication or a fentanyl medication ADDD which has a reservoir (fixed or replaceable) which contains 100 µg of fentanyl or 100 mg of morphine when full, must display both the magnitude and units (e.g. 20 µg of fentanyl or 30 mg of morphine) the operator has selected.

5.1 q): This subclause only applies to ADDDs that have, or allow input from, a reservoir that contains a labelled volume of API from which the operator can select a dose.

The device must inform the operator if the selected dose is larger than the API remaining in the reservoir. This can be done either prospectively or retroactively in two ways:

- Prospectively (before actuation):
  - a selected dose cannot be set at a value that is greater than the dose that is available in the reservoir in the ADDD or
  - the ADDD does not allow any dose delivery if the selected amount exceeds the dose that is available in the reservoir in the ADDD.
- Retrospectively (after actuation):
  - the ADDD indicates the amount of the selected dose actually delivered or
  - indicates the amount of the selected dose not delivered.

For example, an insulin ADDD that has a reservoir (fixed or replaceable) which contains 10 IU of insulin would do the following if the operator requested a 15 IU dose:

- the ADDD would display/indicate a 10 IU dose, only allowing selection of doses at 10 IU or less;
- the ADDD would display 15 IU but not allow actuation unless the dose requested was changed to 10 IU or less;
- the ADDD would allow and display the 15 IU dose before actuation, but would indicate that 10 IU had been delivered after actuation;
- the ADDD would allow and display the 15 IU dose before actuation but would indicate that 5 IU had NOT been delivered after actuation.

Annex B
(informative)

Further guidance and clarification of the device functionality profile

This annex provides further guidance and clarification about the device functionality profile (DFP). This design verification standard applies to the functionality of the device (its components and design) and robustness of ADDD devices. The focus of this DFP is the design function of the ADDD. Once the functionality testing of the ADDD has been completed, verification testing of the delivery performance of the whole ADDD system is required at standard conditions.

ADDDs comprise many different configurations (e.g. pMDIs, DPIs, nasal delivery systems etc.) and there are many different designs within each of these configurations. Further, this array of ADDDs deliver APIs that may be topical (local) or systemic in their site of action with many formulation variations, dose strengths and therapeutic indices. As such the criteria used to demonstrate device functionality may require a number of different test methods that will depend on the ADDD being considered. The device functionality profile including the specific tests for a particular ADDD should be identified through the risk assessment process which will include consideration of the components and materials of the ADDD and their interaction with the medication and interface with the end user.

Some examples of functionality tests are provided here and may include dimensional analysis, mechanical function, actuation etc., see Figure B.1.

Based on the selection of the tests the appropriate protocols may be developed and statistics be applied to demonstrate robust and safe operation of the ADDD after exposure to the storage conditions given in this International Standard.

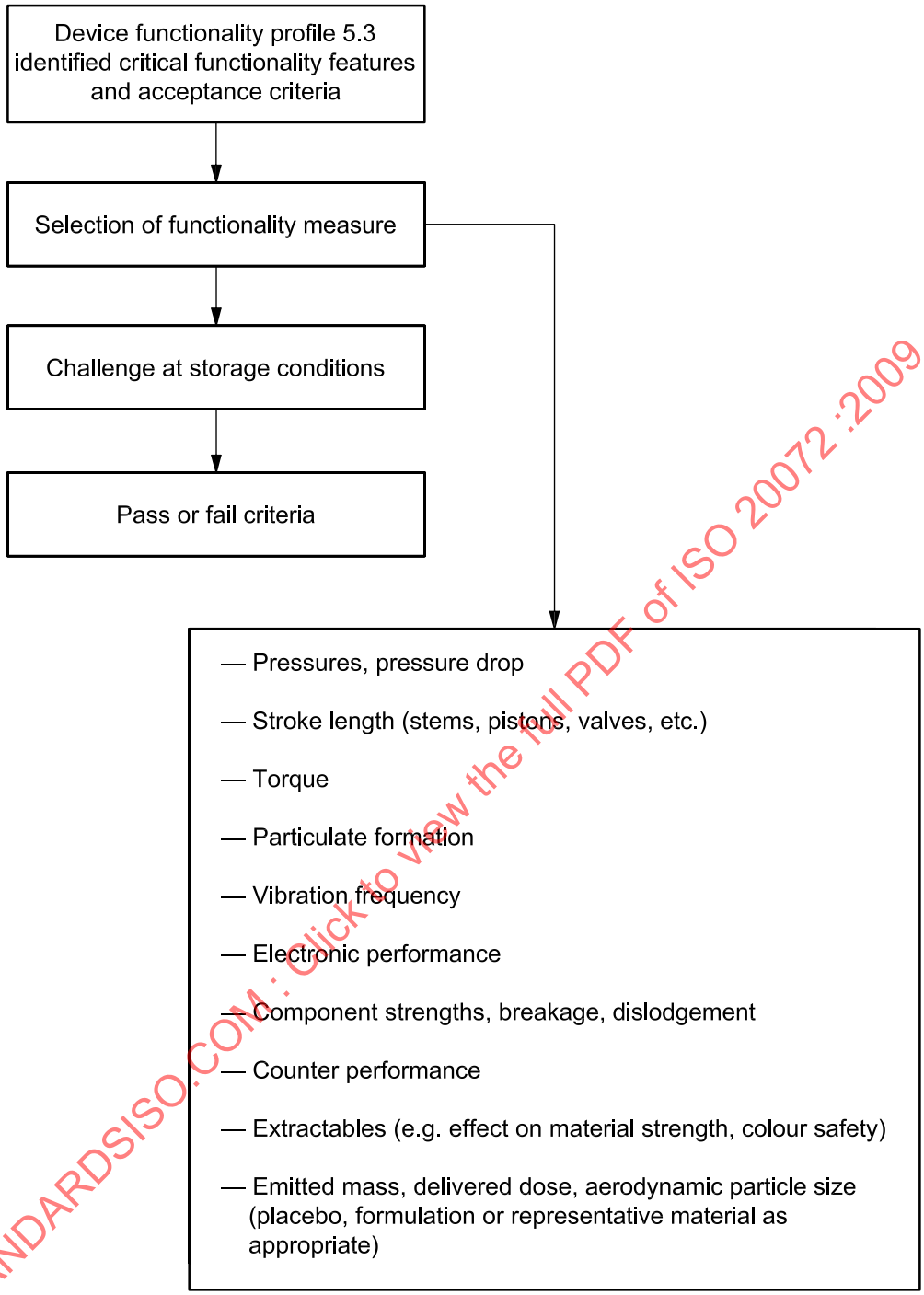

Figure B.1 — Examples of functionality tests

Annex C
(informative)

Rationale for test methods

C.1 Rationale for preconditioning and test conditions (subclauses 6.2 and 6.3)

6.2.6 Free fall

This preconditioning is to simulate accidental dropping of the ADDD by the operator. It is done in compliance with an established IEC standard. The height at which the device can be dropped has been differentiated to adjust the difference in the force of impact caused by the increase in mass or weight. However, manufacturers should use their risk assessments to assure that the height chosen is appropriate for their devices.

6.2.7 Vibration and shock

This preconditioning is to simulate the transport of the ADDD by the operator during normal travel with any caps and/or specified or supplied protective carrying cases. It may also be done without protective materials. It is not a substitute for shipping tests of the final ADDD in its packaging.

6.2.8 EMC

This is a standardized preconditioning scheme for electronic ADDDs to simulate exposure to electromagnetic radiation that may be in the operator environment, including mobile telephones. This is a standard IEC electrical challenge.

6.2.9 Sterilization

This is for ADDDs that will be provided sterile and is included to ensure that the device performs as designed after exposure to the validated sterilization cycle. If the device can be sterilized multiple times, this must be included in the preconditioning.

6.2.10 Cleaning and disinfection

This preconditioning is to simulate the effects of the recommended cleaning and disinfection recommended by the manufacturer so that it can be determined not to adversely affect the performance of the device.

6.2.11 System verification test

Once the ADDD has met the device functionality profile a final holistic system evaluation is conducted at standard atmosphere and nominal flow rate as a simple bridge between the device design and the patient interface; this includes one aerosol measurement per ADDD to confirm the ADDD system functions. If the ADDD is designed to operate over a range of dose sizes, the low, median and high dose size should be evaluated.

6.3.2 Standard atmosphere

The standard atmosphere is the condition at which the testing is performed for all tests except the cool atmosphere and hot atmosphere tests in 6.3.3 and 6.3.4. This environment represents the median or “room temperature” of the labelled use temperature range. Requiring the test samples to remain at specified atmospheres for a minimum of 4 h is to assure equilibration to ambient environmental conditions before testing.

6.3.3 Cool atmosphere

This environment shall represent the low extreme of the labelled[1)] use temperature range. The entire ADDD system[2)] is preconditioned for a minimum of 4 h and tested at this temperature to represent the minimum temperature at which the ADDD is to be used by the patient. The RH is not specified at low temps because the maximum moisture content of the air at 5 °C is about 7 × lower than at 30 °C. The RH is therefore not seen as critical.

6.3.4 Hot atmosphere

This environment shall represent the high extreme of the labelled[2)] use temperature range. The entire ADDD system is to be preconditioned for a minimum of 4 h and tested at this temperature to represent the maximum temperature at which the ADDD is to be used by the patient.

6.3.5 Heat storage atmosphere

This environment shall represent the high extreme of the labelled[2)] shipping and storage temperature range. The entire ADDD system is to be preconditioned at this temperature and then tested in the standard atmosphere to represent the high excursion during shipping and storage.

6.3.6 Cold storage temperature

This environment shall represent the low extreme of the labelled[2)] shipping and storage temperature range. The entire ADDD system is to be preconditioned at this temperature and tested in the standard atmosphere to represent the high excursion during shipping and storage.

6.3.7 Cyclical atmosphere

This extreme environmental conditioning is adapted from an IEC electro-mechanical standard to determine the effects on function of extreme temperature changes which stress component integrity and mechanical and physical interfaces and interactions. The conditions and temperatures are as specified in this International Standard. The lower elevated temperature in the IEC standard has been chosen as more appropriate for the ADDDs.

C.2 Aerosol measurements (subclauses 6.4.2 and 6.4.3)

Emitted mass and, when applicable, the particle size distribution can be assessed by a variety of methods described in the literature. Most commonly it is foreseen that methods applied in the development of ADDDs are the ones equivalent to those accepted by regulatory authorities. These can be as or derived from the test methods described in international Pharmacopeias. There are a number of active Pharmacopeias used today and the appropriate choice of test method depends on the intended place of marketing of the ADDD.

The Pharmacopeias describe the test methods and the parameters obtained as well as the calculations needed for evaluating the aerosol performance of the ADDD. This International Standard only refers to the use of the described test methods. Calculations on the data obtained are covered by this International Standard.

NOTE The statistical evaluation mainly refers to emitted mass. Note also the Pharmacopeial methods determine the API, not emitted mass.

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1) This International Standard allows for use of other less severe conditions as long as these are clearly represented in the labelling. The manufacturer can also elect to test at more extreme conditions.

2) The test samples must be preconditioned and tested in the configuration provided to the customer. If the ADDD is provided pre-filled with the medication, then the test samples must be preconditioned and tested with pre-filled medication or placebo.

Established and recommended methods for the laboratory testing of ADDDs for dose, emitted mass and (aerodynamic) particle size distribution measurement (particle sizing) are available in both European and US Pharmacopeias (see Bibliography). The dose collection apparatus for either pressurized metered dose inhalers or dry powder inhalers (Ph.Eur and US Pharmacopeia) are appropriate for the determination of dose and emitted mass. The testing conditions, especially flow rate, should also be determined as described in the pharmacopeia and the ADDD operated as per the in-use instructions. It is recognised that, for some ADDDs with or without their configured accessories, these apparati have to be modified to permit interfacing of the device and collection apparatus. A multi-stage cascade impactor chosen from the options provided in either pharmacopeia is appropriate for particle size measurements. These methods were developed for the evaluation of ADDDs without a spacer or holding chamber. The number of stages and which ones should be used need to be determined based up on the aerosol size distribution characteristics and specified within the risk assessment.

However, they may be adapted for the evaluation of these add-on devices where required. Methods described in a standard developed specifically for these spacer and holding chamber devices (CAN/CSA/Z264.1-02[13]) are appropriate where it is necessary to evaluate the device functionality profile of the ADDD with this accessory requiring a delay following inhaler actuation.

In all cases the methodology must be validated for the ADDD system under test, to suitable standards.

The methods described in these source documents were developed for in-use testing and might require adaptation (e.g. the use of a climate-controlled enclosure) for application to extreme condition testing.

Alternate methods (e.g. the use of laser diffractometry in place of cascade impaction for particle sizing) may be used for ADDD aerosol measurements, where validated.

Annex D
(informative)

Two-sided tolerance limit factors (k)

Table D.1 — Two-sided tolerance limit factors

n	**Confidence** = 95 %						
	$p = 0{,}750$	$p = 0{,}900$	$p = 0{,}950$	$p = 0{,}975$	$p = 0{,}990$	$p = 0{,}995$	$p = 0{,}999$
2	22,383	31,092	36,519	41,308	46,944	50,813	58,844
3	5,937	8,306	9,789	11,101	12,647	13,710	15,920
4	3,818	5,368	6,341	7,203	8,221	8,921	10,377
5	3,041	4,291	5,077	5,774	6,598	7,165	8,345
6	2,638	3,733	4,422	5,034	5,758	6,256	7,294
7	2,391	3,390	4,020	4,579	5,241	5,697	6,647
8	2,223	3,156	3,746	4,269	4,889	5,316	6,206
9	2,101	2,986	3,546	4,044	4,633	5,039	5,885
10	2,008	2,856	3,393	3,871	4,437	4,827	5,640
11	1,934	2,754	3,273	3,735	4,282	4,659	5,446
12	1,874	2,670	3,175	3,624	4,156	4,522	5,287
13	1,825	2,601	3,093	3,531	4,051	4,409	5,156
14	1,783	2,542	3,024	3,453	3,962	4,312	5,044
15	1,747	2,492	2,965	3,386	3,885	4,230	4,949
16	1,716	2,449	2,913	3,328	3,819	4,158	4,865
17	1,689	2,410	2,868	3,277	3,761	4,095	4,792
18	1,665	2,376	2,828	3,231	3,709	4,039	4,727
19	1,643	2,346	2,793	3,191	3,663	3,988	4,669
20	1,624	2,319	2,760	3,154	3,621	3,943	4,616
21	1,607	2,294	2,731	3,121	3,583	3,903	4,569
22	1,591	2,272	2,705	3,091	3,549	3,865	4,526
23	1,576	2,251	2,681	3,063	3,518	3,831	4,486
24	1,563	2,232	2,658	3,038	3,489	3,800	4,450
25	1,551	2,215	2,638	3,015	3,462	3,771	4,415
26	1,539	2,199	2,619	2,993	3,437	3,744	4,385
27	1,529	2,184	2,601	2,973	3,415	3,720	4,356
28	1,519	2,170	2,585	2,954	3,393	3,696	4,330
29	1,510	2,157	2,569	2,937	3,373	3,675	4,304
30	1,501	2,145	2,555	2,921	3,355	3,654	4,281

Table D.1 (*continued*)

n	**Confidence** = 95 %						
	p = 0,750	p = 0,900	p = 0,950	p = 0,975	p = 0,990	p = 0,995	p = 0,999
31	1,493	2,134	2,541	2,905	3,337	3,635	4,259
32	1,486	2,123	2,529	2,891	3,320	3,617	4,238
33	1,478	2,113	2,517	2,877	3,305	3,600	4,218
34	1,472	2,103	2,505	2,864	3,290	3,584	4,199
35	1,465	2,094	2,495	2,852	3,276	3,569	4,182
36	1,459	2,086	2,484	2,840	3,263	3,555	4,165
37	1,454	2,077	2,475	2,829	3,250	3,541	4,149
38	1,448	2,070	2,466	2,819	3,238	3,528	4,134
39	1,443	2,062	2,457	2,809	3,227	3,516	4,119
40	1,438	2,055	2,448	2,799	3,216	3,504	4,105
41	1,433	2,049	2,440	2,790	3,205	3,492	4,092
42	1,429	2,042	2,433	2,781	3,196	3,482	4,080
43	1,424	2,036	2,425	2,773	3,186	3,471	4,068
44	1,420	2,030	2,418	2,765	3,177	3,461	4,056
45	1,416	2,024	2,412	2,757	3,168	3,452	4,045
46	1,412	2,019	2,405	2,750	3,160	3,443	4,034
47	1,409	2,014	2,399	2,743	3,151	3,434	4,024
48	1,405	2,009	2,393	2,736	3,144	3,425	4,014
49	1,402	2,004	2,387	2,729	3,136	3,417	4,004
50	1,398	1,999	2,382	2,723	3,129	3,409	3,995
51	1,395	1,994	2,376	2,717	3,122	3,401	3,986
52	1,392	1,990	2,371	2,711	3,115	3,394	3,978
53	1,389	1,986	2,366	2,705	3,108	3,387	3,969
54	1,386	1,982	2,361	2,700	3,102	3,380	3,961
55	1,383	1,978	2,356	2,694	3,096	3,373	3,953
56	1,381	1,974	2,352	2,689	3,090	3,367	3,946
57	1,378	1,970	2,347	2,684	3,084	3,361	3,939
58	1,376	1,967	2,343	2,679	3,079	3,355	3,932
59	1,373	1,963	2,339	2,675	3,073	3,349	3,925
60	1,371	1,960	2,335	2,670	3,068	3,343	3,918
61	1,369	1,957	2,331	2,666	3,063	3,338	3,912
62	1,366	1,953	2,327	2,661	3,058	3,332	3,905
63	1,364	1,950	2,324	2,657	3,053	3,327	3,899
64	1,362	1,947	2,320	2,653	3,048	3,322	3,893

Table D.1 (*continued*)

n	**Confidence** = 95 %						
	$p = 0{,}750$	$p = 0{,}900$	$p = 0{,}950$	$p = 0{,}975$	$p = 0{,}990$	$p = 0{,}995$	$p = 0{,}999$
65	1,360	1,944	2,317	2,649	3,044	3,317	3,887
66	1,358	1,941	2,313	2,645	3,039	3,312	3,882
67	1,356	1,939	2,310	2,641	3,035	3,307	3,876
68	1,354	1,936	2,307	2,638	3,031	3,303	3,871
69	1,352	1,933	2,304	2,634	3,027	3,298	3,866
70	1,350	1,931	2,300	2,631	3,023	3,294	3,861
71	1,349	1,928	2,297	2,627	3,019	3,290	3,856
72	1,347	1,926	2,295	2,624	3,015	3,285	3,851
73	1,345	1,923	2,292	2,621	3,011	3,281	3,846
74	1,344	1,921	2,289	2,617	3,008	3,277	3,841
75	1,342	1,919	2,286	2,614	3,004	3,274	3,837
76	1,341	1,917	2,284	2,611	3,001	3,270	3,832
77	1,339	1,914	2,281	2,608	2,997	3,266	3,828
78	1,337	1,912	2,278	2,605	2,994	3,262	3,824
79	1,336	1,910	2,276	2,603	2,991	3,259	3,820
80	1,335	1,908	2,274	2,600	2,988	3,255	3,816
81	1,333	1,906	2,271	2,597	2,984	3,252	3,812
82	1,332	1,904	2,269	2,594	2,981	3,249	3,808
83	1,330	1,902	2,267	2,592	2,978	3,246	3,804
84	1,329	1,900	2,264	2,589	2,975	3,242	3,800
85	1,328	1,899	2,262	2,587	2,973	3,239	3,797
86	1,327	1,897	2,260	2,584	2,970	3,236	3,793
87	1,325	1,895	2,258	2,582	2,967	3,233	3,790
88	1,324	1,893	2,256	2,580	2,964	3,230	3,786
89	1,323	1,892	2,254	2,577	2,962	3,227	3,783
90	1,322	1,890	2,252	2,575	2,959	3,225	3,780
91	1,321	1,888	2,250	2,573	2,957	3,222	3,776
92	1,320	1,887	2,248	2,571	2,954	3,219	3,773
93	1,318	1,885	2,246	2,569	2,952	3,216	3,770
94	1,317	1,884	2,244	2,566	2,949	3,214	3,767
95	1,316	1,882	2,242	2,564	2,947	3,211	3,764
96	1,315	1,881	2,241	2,562	2,944	3,209	3,761
97	1,314	1,879	2,239	2,560	2,942	3,206	3,758
98	1,313	1,878	2,237	2,558	2,940	3,204	3,755
99	1,312	1,876	2,236	2,556	2,938	3,201	3,752

Table D.1 (*continued*)

n	**Confidence** = 95 %						
	p = 0,750	p = 0,900	p = 0,950	p = 0,975	p = 0,990	p = 0,995	p = 0,999
100	1,311	1,875	2,234	2,555	2,936	3,199	3,750
102	1,309	1,872	2,231	2,551	2,931	3,194	3,744
104	1,308	1,869	2,228	2,547	2,927	3,190	3,739
106	1,306	1,867	2,225	2,544	2,923	3,186	3,734
108	1,304	1,864	2,222	2,541	2,919	3,181	3,729
110	1,302	1,862	2,219	2,537	2,916	3,177	3,724
112	1,301	1,860	2,216	2,534	2,912	3,173	3,720
114	1,299	1,858	2,213	2,531	2,909	3,170	3,715
116	1,298	1,855	2,211	2,528	2,905	3,166	3,711
118	1,296	1,853	2,208	2,525	2,902	3,162	3,707
120	1,295	1,851	2,206	2,522	2,899	3,159	3,703
122	1,293	1,849	2,203	2,520	2,896	3,155	3,699
124	1,292	1,847	2,201	2,517	2,893	3,152	3,695
126	1,291	1,845	2,199	2,514	2,890	3,149	3,691
128	1,289	1,843	2,197	2,512	2,887	3,146	3,687
130	1,288	1,842	2,194	2,510	2,884	3,143	3,684
132	1,287	1,840	2,192	2,507	2,881	3,140	3,680
134	1,286	1,838	2,190	2,505	2,878	3,137	3,677
136	1,284	1,837	2,188	2,503	2,876	3,134	3,674
138	1,283	1,835	2,186	2,500	2,873	3,131	3,670
140	1,282	1,833	2,185	2,498	2,871	3,128	3,667
142	1,281	1,832	2,183	2,496	2,868	3,126	3,664
144	1,280	1,830	2,181	2,494	2,866	3,123	3,661
146	1,279	1,829	2,179	2,492	2,864	3,121	3,658
148	1,278	1,827	2,177	2,490	2,861	3,118	3,655
150	1,277	1,826	2,176	2,488	2,859	3,116	3,652
152	1,276	1,825	2,174	2,486	2,857	3,114	3,650
154	1,275	1,823	2,172	2,484	2,855	3,111	3,647
156	1,274	1,822	2,171	2,483	2,853	3,109	3,644
158	1,273	1,821	2,169	2,481	2,851	3,107	3,642
160	1,272	1,819	2,168	2,479	2,849	3,105	3,639
162	1,272	1,818	2,166	2,477	2,847	3,102	3,637
164	1,271	1,817	2,165	2,476	2,845	3,100	3,634
166	1,270	1,816	2,163	2,474	2,843	3,098	3,632
168	1,269	1,815	2,162	2,473	2,841	3,096	3,630

Table D.1 (*continued*)

n	**Confidence** = 95 %						
	p = 0,750	p = 0,900	p = 0,950	p = 0,975	p = 0,990	p = 0,995	p = 0,999
170	1,268	1,813	2,161	2,471	2,840	3,094	3,627
172	1,267	1,812	2,159	2,469	2,838	3,092	3,625
174	1,267	1,811	2,158	2,468	2,836	3,091	3,623
176	1,266	1,810	2,157	2,466	2,834	3,089	3,621
178	1,265	1,809	2,155	2,465	2,833	3,087	3,619
180	1,264	1,808	2,154	2,464	2,831	3,085	3,616
185	1,263	1,805	2,151	2,460	2,827	3,081	3,611
190	1,261	1,803	2,148	2,457	2,823	3,077	3,607
195	1,259	1,801	2,146	2,454	2,820	3,073	3,602
200	1,258	1,798	2,143	2,451	2,816	3,069	3,598
205	1,256	1,796	2,140	2,448	2,813	3,065	3,593
210	1,255	1,794	2,138	2,445	2,810	3,062	3,589
215	1,253	1,792	2,136	2,442	2,807	3,059	3,585
220	1,252	1,790	2,133	2,440	2,804	3,055	3,581
225	1,251	1,789	2,131	2,437	2,801	3,052	3,576
230	1,250	1,787	2,129	2,435	2,798	3,049	3,574
235	1,248	1,785	2,127	2,432	2,795	3,046	3,571
240	1,247	1,783	2,125	2,430	2,793	3,043	3,568
245	1,246	1,782	2,123	2,428	2,790	3,041	3,564
250	1,245	1,780	2,121	2,426	2,788	3,038	3,561
255	1,244	1,779	2,120	2,424	2,786	3,036	3,558
260	1,243	1,777	2,118	2,422	2,783	3,033	3,555
265	1,242	1,776	2,116	2,420	2,781	3,031	3,553
270	1,241	1,775	2,115	2,418	2,779	3,028	3,550
275	1,240	1,773	2,113	2,416	2,777	3,026	3,547
280	1,239	1,772	2,111	2,415	2,775	3,024	3,545
285	1,238	1,771	2,110	2,413	2,773	3,022	3,542
290	1,238	1,770	2,109	2,411	2,771	3,020	3,540
295	1,237	1,768	2,107	2,410	2,769	3,018	3,538
300	1,236	1,767	2,106	2,408	2,767	3,016	3,535
310	1,234	1,765	2,103	2,405	2,764	3,012	3,531
320	1,233	1,763	2,101	2,402	2,761	3,008	3,527
330	1,232	1,761	2,098	2,400	2,758	3,005	3,523
340	1,230	1,759	2,096	2,397	2,755	3,002	3,519

Table D.1 (*continued*)

n	**Confidence** = 95 %						
	$p = 0{,}750$	$p = 0{,}900$	$p = 0{,}950$	$p = 0{,}975$	$p = 0{,}990$	$p = 0{,}995$	$p = 0{,}999$
350	1,229	1,757	2,094	2,395	2,752	2,999	3,515
360	1,228	1,756	2,092	2,392	2,749	2,996	3,512
370	1,227	1,754	2,090	2,390	2,747	2,993	3,509
380	1,225	1,752	2,088	2,388	2,744	2,990	3,505
390	1,224	1,751	2,086	2,386	2,742	2,988	3,502
400	1,223	1,749	2,084	2,384	2,739	2,985	3,499
425	1,221	1,746	2,080	2,379	2,734	2,979	3,493
450	1,219	1,743	2,077	2,375	2,729	2,974	3,486
475	1,217	1,740	2,073	2,371	2,725	2,969	3,481
500	1,215	1,737	2,070	2,368	2,721	2,965	3,476
525	1,213	1,735	2,067	2,364	2,717	2,961	3,471
550	1,212	1,733	2,065	2,361	2,713	2,957	3,466
575	1,210	1,731	2,062	2,358	2,710	2,953	3,462
600	1,209	1,729	2,060	2,356	2,707	2,950	3,458
625	1,208	1,727	2,058	2,353	2,704	2,947	3,455
650	1,207	1,725	2,056	2,351	2,702	2,944	3,451
700	1,204	1,722	2,052	2,347	2,697	2,939	3,445
750	1,202	1,719	2,049	2,343	2,692	2,934	3,439
800	1,201	1,717	2,046	2,339	2,688	2,930	3,434
850	1,199	1,715	2,043	2,336	2,685	2,926	3,430
900	1,198	1,712	2,040	2,333	2,682	2,922	3,426
950	1,196	1,711	2,038	2,331	2,679	2,919	3,422
1000	1,195	1,709	2,036	2,328	2,676	2,916	3,418
1500	1,186	1,697	2,022	2,312	2,657	2,895	3,394
∞	1,150	1,645	1,960	2,241	2,576	2,807	3,291