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Guidance for assessment and evaluation of changes to drug delivery systems

Gestion des changements d'appareils dans les combinaisons de produits pour l'administration de médicaments

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ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Fax: +41 22 749 09 47
Email: copyright@iso.org
Website: www.iso.org

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Foreword

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

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

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

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

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

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Introduction

This document provides guidance to organizations wishing to implement a systematic approach to assess and evaluate changes to needle-based injection systems, needle-free injectors and aerosol delivery devices for medical use (see Clause 1) throughout their lifecycles. In particular, an organization can use the approach for changes to the drug delivery system from entry into pivotal or registration clinical studies through the end of commercial supply.

Due to the breadth of potential change circumstances, this document does not contain prescriptive technical requirements for assessing and evaluating drug delivery system changes but rather provides illustrative guidance for consideration.

This document does not replace or alter existing statutory and regulatory requirements for assessing drug delivery system changes.

Prior to using the process outlined in this document, the organization should have determined the objective of the change including the various opportunities/options for fulfilling the objective.

This document might also be useful for assessing and evaluating change to drug delivery systems other than needle-based injection systems, needle-free injectors and aerosol delivery devices for medical use.

The process can be applied to multiple product lifecycle stages, including design and development, production, storage and distribution, installation, servicing and final decommissioning/disposal of the drug delivery system or associated activities (e.g. up-dating of software). It can also be used by an organization's suppliers and external parties (e.g. raw materials, components, subassemblies, medical devices, sterilization services, calibration services, distribution services, maintenance services).

This document is not intended to replace or alter quality management systems, risk management, or usability engineering requirements in assessing these changes. Rather, it provides a common framework using a scientific and risk-based approach consistent with

— ISO 13485[4],

— ISO 14971[5], and

— IEC 62366-1[8].

Although this process focuses on user safety and drug delivery system performance, it also addresses lifecycle management and includes consideration of appropriate medicinal product guidance (e.g. ICH Q8, ICH Q9, ICH Q10 and ICH Q12). This will help assess the potential impact of changes on the quality, safety, and efficacy of the finished product for the target patient population.

Over the course of a finished product's lifecycle, there will be a broad array of drivers for change. These changes and their various design solutions can be motivated by, but are not limited to the following:

a) adverse event/complaint data;

b) voice of the customer, user feedback or market research;

c) usability studies;

d) changes in processes for production, production scale and supply chain logistics;

e) changes in material or source of supply;

f) impact of changes to the medicinal product that affect the drug delivery system.

This document provides examples of drug delivery system changes using a process flow (see Figure 1). These examples and the conclusions provided are purely illustrative and are intended to provide guidance on how to utilize this document.

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It is the responsibility of organizations to provide evidence that the approach adopted is commensurate with the level of risk to ensure the quality, safety and performance of the drug delivery system. While the focus of this document is the changed drug delivery system, it is also possible that changes to the medicinal product might impact the drug delivery system (e.g. change in viscosity or volume of medicinal product resulting in changed drug delivery system performance). It is also possible that changes to the drug delivery system might impact the medicinal product (e.g. increased injection forces resulting in changed treatment). As such, one key aspect of this process is assessing the change for its potential impact on overall quality given the critical interface between the drug delivery system and the medicinal product. Organizations should evaluate potential impact to the medicinal product in accordance with relevant regulations and guidelines pertaining to medicinal products (e.g. ICH guidelines) to ensure the quality, safety and efficacy.

The core of this document is the process flow, which attempts to guide an organization through a risk-based approach based on drivers of change as mentioned above impacting the

— drug delivery system design,

— manufacturing process, and

— labelling and user interface.

The expectation is that such changes are evaluated through the risk assessment of how the change could impact system form, fit and function (including medicinal product flow paths) such that users are not negatively impacted in terms of quality, safety and performance of the drug delivery system. Given that a single change can affect more than one of the change types (e.g. a material change can also drive a process change), all change types should be assessed and evaluated.

The identification, analysis, evaluation and control of change are common regulatory requirements in the post approval phase of a product's lifecycle, but are also important in the clinical phase of development. Organizations should demonstrate that as the drug delivery system design evolves, the link between the drug delivery system and the medicinal product as tested in the clinical setting (for which market authorization is granted or is intended) is maintained.

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Guidance for assessment and evaluation of changes to drug delivery systems

1 Scope

This document provides guidance for assessment and evaluation of planned changes to drug delivery systems that are integral with, packaged with, or cross-labelled for use with a specified medicinal product. This document is applicable to the drug delivery system's lifecycle from registration clinical studies to end-of-life. This document is applicable to the assessment of changes within the following drug delivery systems:

— needle-based injection systems for medical use;

— aerosol drug delivery devices;

— needle-free injectors for medical use.

NOTE These are covered by the ISO 11608 series, ISO 20072 and ISO 21649, respectively.

This document might also be useful for assessing and evaluate changes to other drug delivery devices or systems.

Examples of changes that are within the scope of this document include but are not limited to the following:

a) the same route of administration (e.g. change resulting in including a marketed prefilled syringe to an autoinjector);

b) changes to the drug delivery system design (e.g. change in configuration or layout of electrical and mechanical components);

c) changes to the medicinal product that affect the drug delivery system; including the primary container closure (e.g. viscosity, particle size);

d) changes in production or handling of the drug delivery system (e.g. process scale, manual to automated assembly, glue bond to sonic weld, mould cavitation, sterilization, storage, transportation, work instructions or methods);

e) changes in component materials or source of supply;

f) changes in software, including changes related to cybersecurity, encryption and connectivity;

g) changes in the user interface, including packaging;

h) changes to labelling and/or instructions for use.

Revisions or additions of software are within the scope of this document. The software can either be integrated into the physical drug delivery system, separate, or both.

The applicability of this document to non-integrated software is relevant to the extent that those software changes can impact the drug delivery system and/or impact how users interact with it.

Depending on the nature of the change, there can be additional assessments and resulting activities, which can be outside the scope of this document.

This document does not provide guidance for defining the objective of the change, nor the various potential opportunities/options for fulfilling this objective.

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2 Normative references

There are no normative references in this document.

3 Terms, definitions and abbreviated terms

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

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

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

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

3.1 Terms and definitions

3.1.1
component
single item, or assembly of items (subassembly) within a *drug delivery system* (3.1.2)

3.1.2
drug delivery system
medical device or system whose primary purpose is the administration of a medicinal product such as drugs and biologics

Note 1 to entry: This term applies to combination of components and subassemblies of the system that are intended to be integrated with the medicinal product with the purpose of providing a method of administration of the medicinal product.

3.1.3
finished product
drug delivery system (3.1.2) and the medicinal product it is intended to deliver

Note 1 to entry: A finished product can be as a single integrated product combining both the drug delivery system and medicinal product as released by its manufacturer. It can also be a drug delivery system and medicinal product that are produced separately and integrated into its final, usable form by the end user.

Note 2 to entry: It is not intended to imply the status of a marketed product or manufacturing responsibility as defined by individual markets.

3.1.4
flow path
pathway the medicinal product or other liquid, gas or powder flow to the targeted site

3.1.5
organization
person or group of people that has its own functions with responsibilities, authorities and relationships to achieve its objectives

Note 1 to entry: The concept of organization includes, but is not limited to, sole-trader, company, corporation, firm, enterprise, authority, partnership, association, charity or institution, or part or combination thereof, whether incorporated or not, public or private.

Note 2 to entry: Regulatory bodies and others can use other terms for organization, such as manufacturer.

[SOURCE: ISO 9000:2015, 3.2.1, modified — the original Note 2 to entry was deleted and a new Note 2 to entry was added.]

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3.1.6
quality
degree to which a set of inherent characteristics of an object fulfils requirements

Note 1 to entry: The term "quality" can be used with adjectives such as poor, good or excellent.

Note 2 to entry: "Inherent", as opposed to "assigned", means existing in the object.

[SOURCE: ISO 9000:2015, 3.6.2]

3.1.7
verification
confirmation, through the provision of objective evidence, that specified requirements have been fulfilled

Note 1 to entry: The objective evidence needed for a verification can be the result of an inspection or of other forms of determination such as performing alternative calculations or reviewing documents.

Note 2 to entry: The activities carried out for verification are sometimes called a qualification process.

Note 3 to entry: The word "verified" is used to designate the corresponding status.

[SOURCE: ISO 9000:2015, 3.8.12]

3.1.8
validation
confirmation, through the provision of objective evidence, that the requirement*s* for a specific intended use or application have been fulfilled

Note 1 to entry: The objective evidence needed for a validation is the result of a test or other form of determination such as performing alternative calculations or reviewing documents.

Note 2 to entry: The word "validated" is used to designate the corresponding status.

Note 3 to entry: The use conditions for validation can be real or simulated.

[SOURCE: ISO 9000:2015, 3.8.13]

3.2 Abbreviated terms

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
App	Application
BSE/TSE	Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathy
IFU	Instructions For Use
PK/PD	PharmacoKinetics/PharmacoDynamics
uFMEA	user Failure Modes and Effects Analysis
pFMEA	process Failure Modes and Effects Analysis
dFMEA	design Failure Modes and Effects Analysis
HFE	Human Factors Engineering
URS	User Requirements Specification
PRS	Product Requirements Specification

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