INTERNATIONAL STANDARD

ISO 20069

First edition
2019-08

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

Reference number
ISO 20069:2019(E)

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

Published in Switzerland

Contents

Page

Foreword

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

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

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

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

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

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

Introduction

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.

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.

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.

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.]

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 requirements 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

API	Active Pharmaceutical Ingredient
pH	potential of Hydrogen, a measure of acidity
cP	centiPoise, a measure of viscosity

4 Process

4.1 General

4.1.1 Process framework

The process outlined in this document provides a framework to assess and evaluate changes to a drug delivery system. It does not provide a framework to assess and evaluate changes to a medicinal product (e.g. reformulation driven by adverse event data). However, if the change to a medicinal product has the potential to impact the drug delivery system (e.g. reformulation increases viscosity impacting delivery forces), then the framework should be used to assess and evaluate the impact on the drug delivery system.

The process is initiated when a change has been proposed for potential implementation. Every change should be assessed based on the individual circumstances of the change. Where multiple changes are occurring simultaneously or concurrently, they should also be assessed for their ability to interfere with each other and/or to collectively impact the product in a manner different to their individual impacts.

The process should be divided into three phases as illustrated in Figure 1:

a) Phase A — Define and assess;

b) Phase B — Execute activities;

c) Phase C — Final evaluation.

Phase A, define and assess, starts with the thorough definition of the proposed change, i.e. the purpose with and scope for the proposed change, a change description including the current state and the proposed state after implementation. The next step is the identification of the change types based on the information collected in the definition step. The last step of this phase is an impact assessment on the performance, safety, stability, compatibility, process, usability, software, clinical data and regulatory compliance.

Phase B, execute activities, consists of two steps, the planning and the execution of the planned activities. During the planning step, all activities that need to be performed in order to prepare a proper implementation of the change should be determined. These activities can include but are not limited to design and development verification, design validation and process validation. The activities depend on the change type (see 4.2.2) and its associated risks and on the specific properties and requirements of the individual change and should be defined on a case by case basis. The planning step is concluded with the confirmation of readiness to perform the planned activities. In the execution step, all the planned activities are performed and completed, e.g. design and development verification work is conducted as per the verification plan established in the planning step. Completion of the activities is a prerequisite for change implementation and to enter the final evaluation Phase C of the change.

Phase C, final evaluation, includes an evaluation supporting a decision as to whether the change should be implemented based on the results obtained in Phase B.

As an organization proceeds through the process, knowledge and perspective obtained through the assessments (e.g. unacceptable risks, non-fulfilment of the objective or unforeseen difficulties in implementing the change) and/or changes in business needs (e.g. cost/time) can result in a decision to not proceed with the change. The basis for the decision should be documented.

Annex A provides an example of a template to guide the assessments and execution of the activities included in Figure 1. Annex B provides examples of completed templates.

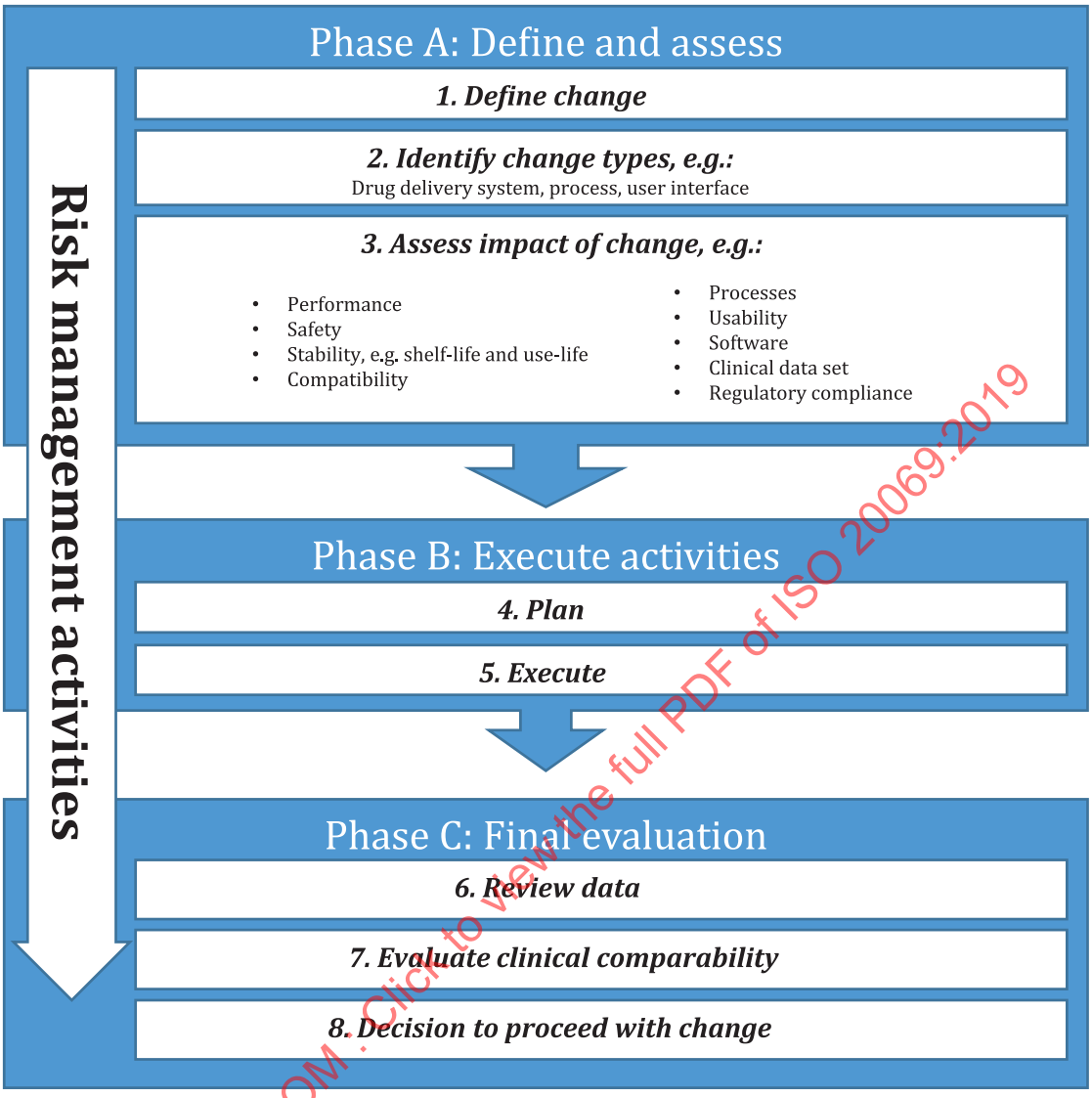

Figure 1 — Process flow for assessment and evaluation of changes to the drug delivery system

4.1.2 Quality and risk management

The process should be performed within the organization's quality and risk management system requirements. This process should be aligned with ISO 13485, in particular control of design and development changes. Risk assessment should be performed and risk controls should be implemented where needed in accordance with ISO 14971 during all phases of this process.

4.1.3 Relationships within the organization and with suppliers or external organizations

Due to the nature of drug delivery systems, it is common for separate functions within a single organization responsible for the drug delivery system to have responsibilities for different aspects of the finished product (e.g. formulation scientists responsible for the medicinal product aspects and device engineers responsible for the drug delivery system aspects). When there is a change to the drug delivery system, it is recommended to define internal roles and responsibilities for the change process and to establish a cross-functional team comprising the relevant levels and functions within the organization to be involved in each phase of this process.

Additionally, it is also common for one or more separate organizations to have responsibilities for different aspects of the product (e.g. component suppliers, medicinal product manufacturer and device manufacturer) and to work collaboratively. Where these relationships exist, it is essential to ensure

that roles and responsibilities with regards to notification of and approval of changes between the parties are defined. Quality agreements with suppliers and other external organizations are one way to ensure that changes that can impact the drug delivery system are transparent to the drug delivery system owner.

Depending on the intended application, changes made within the defined specification range can still be impactful for the drug delivery system. For example, shifting the nominal, as an improvement, within the acceptable range for a particular attribute (e.g. silicone level) can impact the functionality of an injection device. The assessment of this change from a supplier can have no impact as the component still meet specification, but could result in a change in drug delivery system functionality.

4.2 Phase A — Define and assess

4.2.1 Define change (Figure 1, box 1)

This process is about defining the objective for the change and providing a description of the change with the appropriate details. It can also be useful to identify what is not changing (e.g. no change to the primary container and medicinal product flow path).

An objective for the change can include but is not limited to improved safety, improved performance, or substitution of a component.

4.2.2 Identify change types (Figure 1, box 2)

The "current state" and "proposed state" of the drug delivery system as a result of the change should be described. The change types should be identified based on the specifics of the change. The assessments in Table A.1 can be useful to perform the preliminary change type identification.

Given that a single change can fall under more than one of the change types (e.g. a material change can also be a process change), it should be assessed whether the change is included in each of the change type categories to ensure an assessment.

Change types that should be identified include, but are not limited to the following:

a) **Materials**: Change of material of the drug delivery system components or its packaging including, but not limited to, type, grade, chemistry, formulation, additives, colorants, supplier/sub-suppliers, manufacturing materials and/or processing aids.

b) **Form and fit**: Change in physical attributes, such as component dimensions relative to interface/interaction with other components and sub-assemblies.

c) **Function**: Change in system function as defined in the design input requirements and associated design specifications (e.g. dose accuracy, environmental and mechanical robustness, functions that support label claims such as deliverable volume).

d) **Process change**: Change in processes for production and handling of the drug delivery system. Process changes include, but are not limited to changes to the component manufacture, sub-assembly and system assembly processes including the following: process control, packaging, different production sites, sterilization, environmental conditions and storage.

e) **User interface change**: Change impacting the user interface. User interface changes include, but are not limited to changes to the user population, intended users, form factor, packaging, labelling, instructions for use, software, printed materials and training.

f) **Software**: Change to embedded or connected software, including change of separate software that relates to the use of the drug delivery system (e.g. dosing app).

g) **Medicinal product**: Change to the medicinal product that can impact the drug delivery system.

4.2.3 Assess impact of change (Figure 1, box 3)

An assessment should be performed to identify potential impact to design inputs, user requirements and risk control measures to determine whether verification and/or validation activities are required to implement the change. Table A.2 can be a helpful guide when assessing impact of key areas (e.g. performance, shelf-life, clinical evaluation, etc). Based on the assessment, additional verification and/or validation studies should be planned.

For areas that could be potentially impacted by a change, it should be assessed whether existing evidence is adequate to support the change. The assessment should include a review of best available information and objective evidence (data, modelling, literature, etc.).

It should be considered whether the change has the potential to fulfil the objective(s), to cause any new hazard(s), or has the potential to modify the established risk profile and/or the performance of the drug delivery system. Changes should be assessed in relation to potential impact, direct and indirect, on each of

a) the drug delivery system,

b) the medicinal product,

c) the users,

d) manufacturing systems, and

e) compliance with applicable statutory and regulatory requirements.

The assessments should identify required updates of the design and development documentation for the drug delivery system, including, but not limited to drawings, 3-D models, other specifications, software, electronics, hardware, tolerance stack-ups, test equipment, test methods and operating parameters.

4.2.3.1 Assess drug delivery system performance

The drug delivery system performance should be assessed for each type of drug delivery system change. Existing drug delivery system design input requirements should be assessed in order to determine which requirements might be affected or added due to the change. The functional robustness should be assessed – including robustness to shipping, aging, drop, shock, etc.

It should be assessed whether a physical change relates to surfaces that contact the medicinal product liquid or air (in the case of inhaled products). Changes to surface treatments and physical attributes of the drug delivery system components should also be assessed for potential impacts to performance.

A medicinal product change that can potentially impact how the drug delivery system performs should be assessed.

Changes to the interface/interaction with other system components, e.g. sub-assemblies, needles, spacers, primary packaging such as container closures and blisters, and/or other changes of parts/components included in the drug delivery system, should be assessed.

4.2.3.2 Assess safety

It should be assessed whether the change has an impact on the safety of the finished product. Assessments should include, but are not limited to, electrical safety, mechanical safety, biocompatibility, BSE/TSE, material composition (such as whether the material is made with natural rubber, latex, etc.), as appropriate based on the design inputs for the product. Sterility performance should be considered, if applicable.

If the changed material has contact with the medicinal product's flow path, its impact on the quality, safety and performance of the drug delivery system and the quality, safety and efficacy of the medicinal product should be assessed. It should also be assessed whether the material is permitted by applicable

statutory and regulatory requirements (e.g. regulation on restricting the use of hazardous substances, requirements for phthalates, biologically derived materials, bisphenol A (BPA)).

4.2.3.3 Assess drug delivery system stability

For the drug delivery system change, the existing stability testing performed or historical data supporting the stability (e.g. shelf-life and in-use-life) should be assessed. If necessary, additional stability testing to support the change should be performed (e.g. real-time aging, accelerated aging, photo-stability).

4.2.3.4 Assess drug delivery system/medicinal product compatibility

The potential risks associated with types of drug delivery system change that impact how the drug delivery system and medicinal product interact should be assessed.

It should be assessed whether there is a potential impact on the medicinal product's quality attributes, which include physical, chemical, biological, or microbiological properties or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired quality. If the medicinal product quality attributes are potentially impacted, then assessment and evaluation should be performed taking into account relevant regulations and guidelines.

In some organizations, assessments such as container closure integrity, airflow resistance, medicinal product shear, particulates, break loose, extrusion/glide and extractables/leachables can be considered part of the medicinal product characterization. These assessments can also be considered as relating to the drug delivery system.

4.2.3.5 Assess manufacturing processes

It should be assessed if the proposed change potentially impacts the existing process validation. The elements of processes for manufacturing, such as moulding, forming, assembly, sterilization environmental conditions, test methods, equipment should be assessed as well as in-process control and release.

4.2.3.6 Assess usability

The impact on the existing use-related risk assessments and usability data should be assessed to determine whether additional data is needed. Changes to user interface can include, but are not limited to, changes to a component colour, symbols, required user force, labelling, packaging, and software.

NOTE IEC 62366-1 specifies a process for a manufacturer to analyze, specify, develop and evaluate the usability of a medical device as it relates to safety.

4.2.3.7 Assess software

It should be assessed whether the proposed change potentially impacts any software and whether validation of software is needed. This includes any embedded or connected software, including change of separate software that relates to the use of the drug delivery system (e.g. dosing app). Assessment of changes to software should be performed in accordance with IEC 62304.

4.2.3.8 Assess clinical data set

It should be assessed if the change is supported by the existing clinical data set. If not, new clinical data can be needed.

Where the changed drug delivery system is intended to achieve comparability to the unmodified drug delivery system, this review can help identify the type and scope of clinical data necessary to bridge the gap.

EXAMPLE A change in adhesive material could require additional clinical data in relation to skin adherence and irritation.

4.2.3.9 Assess regulatory compliance

It should be assessed if the changed drug delivery system fulfils current, applicable regulatory requirements. If not, appropriate data and documentation should be generated and appropriate measures should be taken. It should be assessed if reporting or submission activities might be needed to maintain or obtain authorization from the competent authority.

4.3 Phase B — Execute activities

4.3.1 Plan (Figure 1, box 4)

Based on the assessments recommended in 4.2.3, the verification and validation activities related to the change should be planned. Table A.2 can be a useful guide in the planning of these activities. The original verification and validation plans, protocols and reports could be used as a guideline. Multiple changes can be verified and/or validated individually and/or in aggregate depending on the risks. Similarly, depending on the risks, change may be planned on the basis of implementation across all elements of the manufacturing systems at once (e.g. all tool cavities, all assembly lines), or piloted at first on a smaller scale. For those areas which have the potential to be impacted by a change, it should be evaluated whether existing evidence for the verification/validation activity is adequate to support the change. If no additional activities are deemed necessary, a justification should be included in the appropriate change management documentation.

Verification and/or validation activities related to the change can include additional design and development verification testing (e.g. in vitro testing), design validation testing (e.g. usability testing, clinical studies) and/or process validation. Some of these activities could potentially be carried out in parallel rather than sequentially, depending on the outcome of risk assessments as appropriate.

If the objective is to establish comparability, then conformance to specifications might not be sufficient. In these circumstances, the statistical and/or clinical differences between the existing and changed drug delivery systems should be considered.

4.3.2 Execute (Figure 1, box 5)

Based on the planning outcomes, implementation, verification and validation related to the change should be executed in accordance with ISO 13485.

Results from the verification and validation activities should be assessed for conformance with the acceptance criteria defined as part of the planning activities recommended in 4.3.1. Additionally, as the organization proceeds through the execution plan, outcomes can identify additional activities needed to support the change.

4.4 Phase C — Final evaluation

4.4.1 General

Final evaluation should be performed to determine whether the data set supports implementation of the change to the drug delivery system.

If any of the evaluations detect new or higher risks, the organization should, at a minimum, conduct a risk/benefit analysis in accordance with ISO 14971 to determine whether the change should be implemented or revisited.

Where the change to the drug delivery system is intended to achieve comparability to the unmodified drug delivery system (e.g. change of resin suppliers for same internal component design), this review process will help determine if existing data and the new data generated is sufficient.

4.4.2 Review data (Figure 1, box 6)

After the change has been verified and validated, the new data along with all existing data from the unmodified drug delivery system relevant to the modified drug delivery system should be reviewed. The aggregated data should support the proposed change. This will include, but is not limited to, clinical data and post-marketing data, both published and internal.

4.4.3 Evaluate clinical comparability (Figure 1, box 7)

If the objective is to establish comparability to the existing clinical data set, then conformance to specifications might not be sufficient.

The modified drug delivery system should be considered comparable to the unmodified drug delivery system if, after assessing all supportive data

a) the modified drug delivery system conforms to the performance specification of the unmodified version,

b) there are no clinically relevant differences between the unmodified and modified versions,

c) the established risk profile of the drug delivery system is not adversely impacted,

d) there are no unresolved gaps between the original and new data sets, and

e) there are no new safety or performance issues.

If comparability is not established, the organization should determine what, if any, additional clinical data are needed to support proceeding with the change.

4.4.4 Decision to proceed with change (Figure 1, box 8)

Based on the evaluation of the change to the modified drug delivery system, a decision to proceed or discontinue the change should be made and documented. The last section of Table A.3 can be useful to document this decision. Any reporting or submission activities needed to obtain authorization from the competent authority should be performed prior to implementation of the change.

Annex A
(informative)

Templates

The templates given in Annex A are provided as guidance for assessing, evaluating and documenting a change decision. The framework, structure, and details are suggestions only. They are not exhaustive and should be refined based upon the nature of the change under consideration. The templates are organized and designated to reflect the process as defined in Figure 1.

Table A.1 is intended to provide an overview for defining, identifying and assessing a change (see 4.2 and Figure 1, Phase A, boxes 1, 2 and 3). It identifies the type of change as described in 4.2.2 and comprises the impact assessment as described in 4.2.3.

Table A.2 is intended to capture the initial assessment of potential impact based on the change and then be updated to document the results from the verification and validation activities defined and executed (see 4.3 and Figure 1, boxes 4 and 5).

Table A.3 is intended to capture the final evaluation of the change (see 4.4 and Figure 1, boxes 6, 7 and 8) considering all available data. Finally, based on review of the data, a decision of whether or not to proceed with the change as described in 4.4.4 should be documented.

Table A.1 — Template for defining, identifying and assessing a change

<table>
<tr><th colspan="3">Phase A — Define and assess (Figure 1, boxes 1, 2 and 3)</th></tr>
<tr><td colspan="3">Name of change (brief designation)
Instructions: Designate/name the change and scope of change for identification purposes.</td></tr>
<tr><td colspan="3">1. Define change
Instructions: Define the objective for the change and provide a description of the change with appropriate details, e.g. increased safety, increased performance of the drug delivery system or need to substitute a component of the drug delivery system. It can also be useful to identify what is not changing.</td></tr>
<tr><td colspan="3">2. Identify change type(s)
Instructions: Describe the change in appropriate detail and classify each change type, e.g. materials, form and fit, function, process, user interface, software, medicinal product. There can be other change types.
Be sure to describe the “current state” and “proposed state”. Indicate in this section if the change involves a pre-planned change to performance (e.g. injection time change).
A tabular listing such as the following can be utilized as appropriate:</td></tr>
<tr><td>Current state
(changed from)</td><td>Proposed state
(changed to)</td><td>Change type</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td colspan="3">3. Assess impact of change
Instructions: Consider the following attributes and data package(s) in view of the change(s) being proposed and whether the existing data which supports the registered finished product is potentially impacted based upon modifying the drug delivery system:
— performance (including functionality, robustness, surfaces/interface that contact the medicinal product or other system components);
— safety (electrical, mechanical safety, biocompatibility, maintenance of sterility);
— stability (shelf-life and in-use life);</td></tr>
</table>

Table A.1 *(continued)*

Phase A — Define and assess (Figure 1, boxes 1, 2 and 3)
— *compatibility (medicinal product/drug delivery system and impact to medicinal product quality attributes);* — *processes (in-process control, sterilisation, environmental conditions as well as process validation);* — *usability (including human factors);* — *software (interfacing software and validation status);* — *clinical data set evaluation (consider the applicability of the existing data set to support the modified drug delivery system);* — *regulatory compliance.* *It is recommended that Table A.2 be used to summarize this assessment and rationale, as to whether further assessments are necessary or not.*

Table A.2 — Template for assessment and documented evidence for a change

Impact of change, planning and execution of activities				
Instructions: It is recommended this table be used in sequence for Phase A — Define and assess, then updated to capture Phase B, summarizing the executed activities. For each assessment, it should capture the evaluation of what the potential impact of the change could be as a result, and record as Yes or No in the impact column. A description of proposed activities (e.g. for verification and validation) to support the change(s) is recommended. Any justification for not performing further activities should also be captured in the rationale column. Following execution of the activities in Phase B, the evidence of completion should be listed (e.g. performance study report, process validation reports, usability reports) in the documented evidence/summary of completion column, to be subsequently used as part of the final assessment. A given change can impact more than one change type.				
Phase A — Define and assess (Figure 1, boxes 1, 2 and 3)			**Phase B — Execute activities (Figure 1, boxes 4 and 5)**	
Assessment (Figure 1, box 3), e.g. not exhaustive	**Assessment of potential impact YES/NO**	**Rationale**	**Planned execution activities**	**Documented evidence/Summary of completion**
Drug delivery system performance	YES ☐ NO ☐			
Safety	YES ☐ NO ☐			
Drug delivery system stability	YES ☐ NO ☐			
Drug delivery system/ medicinal product compatibility	YES ☐ NO ☐			
Processes	YES ☐ NO ☐			
Usability	YES ☐ NO ☐			
Software	YES ☐ NO ☐			
Clinical data set	YES ☐ NO ☐			
Regulatory compliance	YES ☐ NO ☐			

Once the execution work has been performed, a final assessment of all the data and information is undertaken to determine whether the existing data for the unmodified drug delivery system is impacted. This data is not limited to drug delivery system performance or clinical evaluation, but should include post-marketing experience and other internal data.

In the case where the modified drug delivery system is not considered comparable to the unmodified system and there is an impact on the existing data set, consideration should be given as to whether further clinical evaluation(s) are needed.

Table A.3 — Template for the final evaluation

Phase C — Final evaluation
6. Review data *Instructions: It should be evaluated whether the available data supports implementation of the modified drug delivery system. After the change has been verified and validated, all information available that supports the implementation of the unmodified finished product should be reviewed (e.g. clinical data, post-marketing experience, published data and internal data) for continued applicability to the modified drug delivery system.* Impacted? YES ☐ NO ☐ Rationale:
7. Evaluate clinical comparability *Instructions: Determine the impact to the existing clinical data set using the list given in 4.2.3 and determine whether there are gaps in the available data to support the clinical safety and efficacy of the modified finished product.* Is clinical testing required? YES ☐ NO ☐ Rationale:
8. Decision to proceed with change Proceed with change? YES ☐ NO ☐ Rationale: *Instructions: Any reporting or submission activities needed to obtain authorization from the competent authority should be performed in accordance with applicable statutory and regulatory requirements prior to implementation of the change.*

Annex B
(informative)

Example of completed templates for assessing and evaluating a change

B.1 Example for assessing and evaluating a component colour change

This clause provides an example of completed templates for assessing and evaluating changes to a component colour of a pen-injector cartridge holder.

The examples (see Tables B.1 to B.3) and the conclusions provided are purely hypothetical and should not be interpreted to obviate the critical interactions between organizations and regulators, who ultimately determine whether additional data is required to support the proposed change.

Table B.1 — Completed template for defining, identifying and assessing a component colour change of a pen-injector cartridge holder

<table>
<tr><td colspan="3">Name of change:
Change of colour of pen-injector cartridge holder (change reference xxxx).</td></tr>
<tr><td colspan="3">Phase A — Define and assess</td></tr>
<tr><td colspan="3">1. Define change
The current design of a marketed pen-injector (the drug delivery system) includes a clear cartridge holder regardless of the medicinal product contained in the pen-injector. The objective of the change is to improve the ability of a user to distinguish between variants of one type of pen-injector containing different medicinal products. The chosen opportunity to fulfil the objective is to introduce a range of colours for the cartridge holder component, i.e. one dedicated colour per medicinal product.
A total of five colours have been proposed in addition to the current clear cartridge holder.
The following details of the pen-injector are NOT changing:
— intended use for the drug delivery system;
— any other components or materials;
— the medicinal product (API, formulation and volume in container);
— the intended patient population for each medicinal product;
— the route and method of administration;
— the manufacturing process and assembly sequence.</td></tr>
<tr><td colspan="3">2. Identify change type(s)
The following has been identified as changing:</td></tr>
<tr><td>Current state
(changed from)</td><td>Proposed state
(changed to)</td><td>Change type</td></tr>
<tr><td>Clear colour cartridge holder.</td><td>Cartridge holder component available in a range of six (five + original clear) colours for individual medicinal product specific pen-injectors, by means of addition of master batch colours.</td><td>Materials.</td></tr>
</table>

Table B.1 *(continued)*

Component moulded in a clear material.	Component moulded in a range of six (five + original clear) colours by means of addition of master batch colour to same base material.	Process.
One pen-injector variant used in the final assembly process regardless of medicinal product type.	Range of six (five + original clear) coloured cartridge components specific to a pen-injector used in final assembly.	Process.
Instructions for use and packaging are the same with no differentiation between pen-injectors.	Instructions for use and packaging modified to incorporate different colours for individual medicinal product pen-injectors.	User interface.

3. Assess impact of change

A preliminary risk assessment regarding the impact of the material change was completed. It concluded the following could potentially be impacted:

Drug delivery system performance

— Risk to performance of the component under drop test conditions due to possible change in mechanical properties of cartridge holder. Performance is unaffected providing that the components are validated within tolerance.

Safety

— A material change will drive the need for further biological evaluation of this component as it is user (skin) contacting.

Stability

— Possible change in mechanical properties can require retest of shelf and in-use life unless alternative mechanical testing can provide sufficient proof of equivalence to original clear component. As this is considered low risk (base material remains the same), this change is considered subject to mechanical testing, together with new real-time stability testing.

Drug delivery system/medicinal product compatibility

— The material change to the cartridge holder is not a medicinal product/primary package change, therefore no impact on medicinal product stability, packaging and container closure integrity, handling, or medicinal product manufacturing process.

— The change can impact needle attachment compatibility.

Processes

— Plastic injection moulding – Impact to tool and component validation. As base material is not changing and if an initial assessment of the additional coloured components shows they can meet the current component specification and demonstrate dimensional equivalence, then full process validation may not be required. All selected colours to be permitted should demonstrate equivalence or require process validation.

— Automated assembly – Impact to assembly validation. Additional colours require validation of all affected assembly systems including sensors and vision systems. Visual quality of output components need to be verified. Quality control and specifications requires updating to ensure correct medicinal product is associated with correct colour. This assembly process update requires process validation.

— Test methods – Design and production test methods have been assessed for impact and determined to be unaffected. No test sensors or test processes are affected by the colour change.

Table B.1 *(continued)*

Usability — A change from a clear component to a range of colours can impact user understanding of the pen-injector and which finished product they are using. Risk is significant as the colour is intended to help the user differentiate between variants of one drug delivery system. A further usability validation specific to the change will be required to include intended changes. Visibility of the medicinal product is unaffected as the design of the component itself is unchanged and the component has a large open viewing window to view the appearance of the medicinal product. **Software** — The pen-injector is a mechanical drug delivery system. No software used. **Clinical data set** — As the medicinal product and its interfaces to the pen-injector and the user are not changed by the component colour change, the clinical dataset related to the medicinal product is not changed. — Any clinical data set pertaining to each specific pen-injector should be evaluated in relation to the design change. **Regulatory compliance** — Relevant authorities should be informed regarding the change.

Table B.2 — Completed template for assessment and documented evidence for a component colour change of a pen-injector cartridge holder

Impact of change, planning and execution of activities				
As part of the execution for each of the steps in this process, documentation in accordance with ISO 13485 and ISO 14971 should be performed. Consideration and control of risk for a given change should be made as part of the change assessment and evaluation of the impact to the drug delivery system. An overall risk assessment for the change will be made as part of the final assessment (Table B.3) when evaluating the impact to drug delivery system and existing data set.				
Phase A — Define and assess (Figure 1, boxes 1, 2 and 3)			**Phase B — Execute activities (Figure 1, boxes 4 and 5)**	
Assessment (Figure 1, box 3), e.g. not exhaustive	**Assessment of potential impact YES/NO**	**Rationale**	**Planned execution activities**	**Documented evidence/Summary of completion**
Drug delivery system performance	YES ☑ NO ☐	Change in material composition due to additional colours.	Mechanical drop testing.	Drop test report.
Safety	YES ☑ NO ☐	Change in material in skin contact.	Biocompatibility all additional colours.	Biocompatibility rationale and report.
Drug delivery system stability	YES ☑ NO ☐	Change in materials possibly altering shelf/use life characteristics.	Mechanical materials testing via test samples. New real-time stability schedule commenced.	Materials testing report. Accelerated aging report. Real time stability protocol (report not available – testing real time).
Drug delivery system/medicinal product compatibility	YES ☑NO ☐	No medicinal product contact. Minor dimensional changes can affect needle attachment compatibility.	Needle attachment compatibility.	Needle compatibility report.
Processes	YES ☑ NO ☐	Change of material in injection moulding process. Addition of new colours in auto-assembly.	Moulding equivalence testing. Auto-assembly sensor validation and process reverification.	Moulding equivalence report. Colour 3 validation report (Colour 3 failed equivalence testing and required new process settings and subsequent validation). Auto-assembly validation report.
Usability	YES ☑ NO ☐	Additional colours associated with medicinal product type.	Usability evaluation.	Usability evaluation report.
Software	YES ☐ NO ☑	No software as part of pen-injector.	Not applicable.	Not applicable.
Clinical data set	YES ☐ NO ☑	Evaluate according to existing clinical data set.	None required.	None required.
Regulatory compliance	YES ☑ NO ☐	According to local authority requirements.	Per authority requirements.	Per authority requirements.

Table B.3 — Completed template for the final evaluation of a component colour change of a pen-injector cartridge holder

Phase C — Final evaluation
6. Review data Impacted? YES ☐ NO ☑ Usability evaluation concluded that together with the proposed changes to instructions for use (IFU) and packaging, the users were able to safely distinguish and recognize different products using the colour differences on the cartridge holder component and respective IFU and packaging versus the original non-coloured cartridge holder component with no respective differentiation on the packaging or IFU. The drug delivery system performance was shown to be equivalent and meet current specifications as well as ISO 11608-1 requirements.
7. Evaluate clinical comparability *Instructions: Determine the impact to the existing clinical data set using the list given in 4.2.3 and determine whether there are gaps in the available data to support the clinical safety and efficacy of the modified finished product.* Is clinical bridging required? YES ☐ NO ☑ Rationale: Based on equivalent performance of the pen-injector, further clinical studies are not required. The completed evaluation shows that the current clinical data set is not impacted by the change to the pen-injector.
8. Decision to proceed with change Proceed with change? YES ☑NO ☐ Rationale: All verification and validation activities have been completed and demonstrate that the impact of the change has been fully and properly assessed and the potential risks have been mitigated. Risk management files should be updated immediately prior to implementation of the change. *Instructions: Any reporting or submission activities needed to obtain authorization from the competent authority should be performed in accordance with applicable statutory and regulatory requirements prior to implementation of the change.*

B.2 Example for assessing needle-free injector change

This clause provides an example of completed templates for assessing, evaluating and documenting changes to a needle-free injector.

The examples (see Tables B.4 to B.6) and the conclusions provided are purely hypothetical and should not be interpreted to obviate the critical interactions between sponsors and regulators, who ultimately determine whether clinical data is required to support the proposed change.

Table B.4 — Completed template for defining, identifying and assessing a needle-free injector change

Name of change: Change from reusable spring-powered needle-free injector to an electromechanically-powered injector (Change reference xxxx).		
Phase A — Define and assess		
1. Define change A reusable spring-powered needle-free injector has a two-year in-use life. Market data suggests that the needle-free injector would be more attractive to users if it had a four-year in-use life. However, given the limitations of the spring (e.g. fatigue over time), the back-end of the needle-free injector will have to be re-designed to utilize an electromechanical drive system capable of reliable durability over time. The front end of the needle-free injector (i.e. the medicinal product container/fluid path) and the filling of the container by the user are to remain identical to the spring-driven version. It is also desirable that the energy profile and the depth and dispersion curves (i.e. the performance profile) remain equivalent to that obtained from the spring-driven version in an effort to avoid additional clinical data, given prior successful mapping of the performance profile to the desired clinical pharmacology (PK/PD). The following aspects of the existing spring-powered drug delivery system NOT changing: — intended user population, indication, and route of administration; — the medicinal product container or the medicinal product to be administered; — the user interface for filling the medicinal product reservoir (i.e. front-end of the needle-free injector); — the user interface for attaching the medicinal product reservoir to the back-end (i.e. drive mechanism); — the performance profile and its relationship to the desired clinical pharmacology (PK/PD).		
2. Identify change type(s) The proposed change extends to numerous change categories referred to in this document:		
Current state (changed from)	**Proposed state (changing to)**	**Change type**
Design, materials, form factor of the back-end of the existing needle-free injector, based around re-usable spring power technology.	Design, materials, form factor of the back-end of the re-designed needle-free injector, based around re-usable electromechanical drive system.	Materials.
Design, materials, form factor of the back-end of the existing needle-free injector, based around re-usable spring power technology.	Design, materials, form factor of the back-end of the re-designed needle-free injector, based around re-usable electromechanical drive system.	Form and fit.
Design, materials, form factor of the back-end of the existing needle-free injector, based around re-usable spring power technology.	Design, materials, form factor of the back-end of the re-designed needle-free injector, based around re-usable electromechanical drive system.	Function.
Design, materials, form factor of the back-end of the existing needle-free injector, based around re-usable spring power technology.	Design, materials, form factor of the back-end of the re-designed needle-free injector, based around re-usable electromechanical drive system.	Process.
User interface for the back-end of the existing spring-powered needle-free injector.	User interface for the back-end of the re-designed electromechanically driven needle-free injector.	User interface.
Instructions for use and secondary packaging for the spring-powered needle-free injector.	Instructions for use and secondary packaging for the re-designed electromechanically driven needle-free injector.	User interface.

Table B.4 *(continued)*

No software in the current spring-powered needle-free injector.	Software required as part of introduction of electro-mechanical drive system.	Software.
Design input requirements for the existing spring-powered needle-free injector e.g. Two-year in-use product lifetime.	Design input requirements for the re-designed electromechanically driven needle-free injector e.g. four-year in-use product lifetime.	Function.

3. Assess impact of change

A preliminary risk assessment was completed to review the impact of changes to input requirements, finished product, process and user interface. In summary this concluded that:

Drug delivery system performance

— The design input requirements would need to be revised to reflect the new technology of the electromechanical subassembly, and new requirements added.

— The performance of the new back-end design would need to be verified against new and existing requirements.

— The new performance profile would need to be verified to ensure no change from the existing profile (with acceptance criteria for 'no change' to be defined).

Safety

— An update to the risk assessments (uFMEA, dFMEA, and pFMEA) would be required, with additional risk assessment required relating to electronics and software elements. An updated risk management plan would be required.

— Additional material biocompatibility testing was necessary as the user contacting materials of the back-end of the needle-free injector were changed.

Stability

— The change to in-use product lifetime from two years to four years meant that needle-free injector functional stability/shelf life assessments (accelerated and real time) would need to be performed even for aspects of the design which had not changed.

Drug delivery system/medicinal product compatibility

— Due to the fact there were no changes to the primary container, medicinal product formulation, or medicinal product fluid path, no new medicinal product stability or compatibility assessments would need to be performed (shelf life of drug contact components remains less than two years.)

— Primary container and medicinal product path are not affected nor is any other feature of the needle-free injector associated with delivery of the medicinal product. Hence the risk assessment suggested that additional PK/PD assessments would be unlikely, which is to be confirmed through successful design verification.

Processes

— Given the redesign of the drive mechanism, form factor, associated components and assembly, further process validation would be required.

— Sterilization validation was not impacted as the change doesn't impact the sterile barrier or medicinal product contacting components (shelf life of medicinal product contact components remains less than two years).

Usability

— New usability formative/summative assessments would be required as the design change modifies the specific way the user interacts with the needle-free injector. A new or updated usability engineering (HFE) plan would outline the approach and updated/new documentation generated as required.

— Some additional or repeat validation activities would be required as a result of updated design inputs.

Table B.4 *(continued)*

Software — Software validation would be required due to the addition of the electromechanical design, including full documentation of the software development. **Clinical data set** — The original clinical data set is to be reviewed to confirm that the original needle-free injector and its performance profile included sufficient testing within the full range of the profiles pertinent specification limits such that the variability in the new performance profile, while not identical, falls within the original specification limits. If this is the case it might be justified to argue that the original clinical data set is still valid though the review will need to confirm this. **Regulatory compliance** — Although it is possible that additional clinical data will not be required, compliance with other regulatory/submission requirements will not necessarily be met, for example due the changed nature of the needle-free injector or the fact that regulatory requirements may have changed since the original submission. Some impact on regulatory compliance is to be expected.

Table B.5 — Completed template for assessment and documented evidence for a needle-free injector change

Impact of change, planning and execution of activities				
As part of the execution for each of the steps in this process, documentation in accordance with ISO 13485 and ISO 14971 should be performed. Consideration and control of risk for a given change should be made as part of the change assessment and evaluating impact to the drug delivery system. An overall risk assessment for the change will be made as part of the final assessment (Table B.6) when evaluating the impact to drug delivery system and existing data set.				
Phase A — Define and assess (Figure 1, boxes 1,2 and 3)			**Phase B — Execution activities (Figure 1, boxes 4 and 5)**	
Assessment (Figure 1, box 3), e.g. not exhaustive	**Assessment of potential impact YES/ NO**	**Rationale**	**Planned execution activities**	**Documented evidence/Summary of completion**
Drug delivery system performance	YES ☑ NO ☐	Significant changes made to needle-free injector design and construction, and to product requirements.	Design verification to be carried out for modified design, to updated design inputs.	Design verification plan, test protocols and report, design verification summary reports. See also updated design input documents (URS, PRS).
Safety	YES ☑ NO ☐	Biocompatibility testing is necessary as the user contacting materials of the back-end of the needle-free injector are changing. Electrical safety testing is required due to addition of electro-mechanical drive system.	Biocompatibility testing for new patient contacting (intact skin) components or risk assessment based on ISO 10993-1 requirements. Electrical safety to be carried out to IEC 60601-1. Additional risk assessment activities to ISO 14971.	Biocompatibility study reports. Electrical safety testing reports. Updated risk management file.
Stability	YES ☑ NO ☐	Change in requirements included a significant increase in needle-free injector shelf-life. No change to primary pack or medicinal product formulation, therefore no impact to medicinal product quality or shelf-life.	Design verification included assessment of needle-free injector over new extended in-use life (four years).	Design verification plan, test protocols and report, design verification summary report. See also updated design input documents (URS, PRS).
Drug delivery system /medicinal product compatibility	YES ☐ NO ☑	No change to primary pack or medicinal product formulation.	None required.	None required.
Processes	YES ☑ NO ☐	Significant changes made to production processes, including new tooling and methods of manufacture.	Complete further process validation for new and updated manufacturing processes for back-end of needle-free injector.	Validation plan and summary reports.

Table B.5 *(continued)*

Impact of change, planning and execution of activities				
Usability	YES ☑ NO ☐	Design changes have modified some of the ways in which the user interacts with the needle-free injector. Further validation study will be required to demonstrate safe and effective use of the needle-free injector and interface materials including IFU.	Further usability engineering (HFE) work, including risk assessment activities, to demonstrate that the modified needle-free injector can also be used safely and effectively with no significant new risks introduced. Update IFU to reflect revised user steps for new needle-free injector. Carry out further validation study to demonstrate safe and effective use of the needle-free injector and interface materials including IFU.	Updated usability engineering plan, summary report and additional documentation. Updated risk management file. Updated IFU. Validation study report,
Software	YES ☑ NO ☐	Software has been introduced to the needle-free injector.	Software validation to be carried out in line with applicable standard(s).	Software development documentation including validation report.
Clinical data set	YES ☐ NO ☑	No additional clinical data required.	None required.	None required.
Regulatory compliance	YES ☑ NO ☐	Full needle-free injector submission/assessment required.	Per authority requirements.	Per authority requirements.

Table B.6 — Completed template for a final evaluation of a needle-free injector change

Phase C — Final evaluation
6. Review data Impacted? YES ☐ NO ☑ Rationale: Design verification work demonstrated that all drug delivery system requirements were met and that the performance profile (i.e. energy profile and the depth and dispersion curves) for the modified electromechanically powered needle-free injector was equivalent to the spring powered needle-free injector. The medicinal product container/fluid path and the filling of the container by the user are identical for both versions. Final risk assessment summary report indicated no unacceptable residual risks for the modified needle-free injector. Usability engineering (HFE) summative assessments demonstrated that the modified needle-free injector can be used safely and effectively.
7. Evaluate clinical comparability *Instructions: Determine the impact to the existing clinical data set using the list given in 4.2.3 and determine whether there are gaps in the available data to support the clinical safety and efficacy of the modified finished product.* Is clinical bridging required? YES ☐ NO ☑ Rationale: Based on the equivalent performance data and usability assessments, the current clinical data set is not impacted.
8. Decision to proceed with change Proceed with change? YES ☑ NO ☐ Rationale: Assessment confirmed no impact on quality, safety and performance of needle-free injector, therefore no requirement for clinical bridging. Rationale for change remains valid. *Instructions: Any reporting or submission activities needed to obtain authorization from the competent authority should be performed in accordance with applicable statutory and regulatory requirements prior to implementation of the change.*

B.3 Example of assessing a primary container material change

This clause provides an example of completed templates for assessing, evaluating and documenting a primary container material change in a dry powder inhaler.

The examples (see Tables B.7 to B.9) and the conclusions provided are purely hypothetical and should not be interpreted to obviate the critical interactions between sponsors and regulators, who ultimately determine whether clinical data is required to support the proposed change.

Table B.7 — Completed template for defining, identifying and assessing a primary container material change in a dry powder inhaler

Name of change: Primary container material change (change reference xxxx).
Phase A — Define and assess
1. Define change The elastomer material of the primary medicinal product container for a dry powder inhaler is to be changed. The alternative elastomer material is to be sourced from an alternative supplier and as a result of the change in material, the injection moulding process for the primary medicinal product container will also change to accommodate the new material being used. The following details of the dry powder inhaler are NOT changing: — user interface will not be changed;

Table B.7 *(continued)*

<table>
<tr><td colspan="3">Name of change:
Primary container material change (change reference xxxx).</td></tr>
<tr><td colspan="3">— no changes of the filling of the primary medicinal product container or assembly process of the inhaler with the primary medicinal product container;
— the drug (API, formulation and volume in container);
— the indication or intended patient population;
— the route of administration.</td></tr>
<tr><td colspan="3">2. Identify change type(s)
The category of this change is summarised as follows:</td></tr>
<tr><td>Current state
(changed from)</td><td>Proposed state
(changed to)</td><td>Change type
(drug delivery system/process/user interface)</td></tr>
<tr><td>Medicinal powder container moulded from elastomer A.</td><td>Medicinal powder container moulded from elastomer B.</td><td>Material.</td></tr>
<tr><td>Material supplier X.</td><td>Material supplier Y.</td><td>Material.</td></tr>
<tr><td>Injection moulding process 1.</td><td>Injection moulding process 2.</td><td>Process.</td></tr>
<tr><td colspan="3">3. Assess impact of change
A preliminary risk assessment regarding the impact of the elastomer material change concluded the following could potentially be impacted:
Drug delivery system performance
— On the basis that material properties of the primary medicinal product container could be different. As such this could influence how the medicinal product interacts with the container, transfer of powder static and aerosolisation.
Safety
— Different elastomer material could have different chemical stability, as well as different potential extractables and leachables profile.
Stability
— Based on the chemical profile and stability of the elastomer, the shelf-life/use-life can be impacted.
Drug delivery system/medicinal product compatibility
— There could be potential impact on the medicinal product critical quality attributes based on a different extractable/leachable profile which could affect chemical stability and degradation.
Processes
— Assembly of the primary medicinal product container with the inhaler could be impacted based on different material properties of the elastomer and therefore further process validation could be required.
Usability
— As no key user interface elements or user steps of the dry powder inhaler are altered by the proposed change, no user performance, information or prior validation studies are impacted.
Clinical data set
— A change in the medicinal product elastomer material has the potential to affect the aerosol performance and therefore the bioavailability. This could impact the clinical data set.
Regulatory compliance
— As a consequence of several medicinal product/device interface elements relating to performance and material compatibility being affected, regulatory compliance could be impacted and should be assessed.</td></tr>
</table>

Table B.8 — Summary of assessment and documented evidence for a primary container material change in a dry powder inhaler

Impact of change, planning and execution of activities				
As part of the execution for each of the steps in this process, documentation in accordance with ISO 13485 and ISO 14971 should be performed. Consideration and control of risk for a given change should be made as part of the change assessment and evaluating impact to the drug delivery system. An overall risk assessment for the change will be made as part of the final assessment (Table B.9) when evaluating the impact to drug delivery system and existing data set.				
Phase A — Define and assess (Figure 1, boxes 1,2 and 3)			**Phase B — Execution activities (Figure 1, boxes 4 and 5)**	
Assessment (Figure 1, box 3), e.g. not exhaustive	**Assessment of potential impact YES/NO**	**Rationale**	**Planned execution activities**	**Documented evidence/Summary of completion**
Drug delivery system performance	YES ☑ NO ☐	The elastomer of the primary medicinal powder container is changed which has the potential to change the physical properties of the powder and ability to aerosolize.	Design verification.	Design verification plan, test protocols and report, design verification summary report.
Safety	YES ☑ NO ☐	The elastomer of the primary medicinal powder container is changed and therefore, as it is medicinal product contacting, further biocompatibility assessments would be required to accept the safety of the material to ISO 10993 or equivalent requirements.	Biocompatibility testing for medicinal product contacting components or risk assessment based on ISO 10993-1 requirements.	Biocompatibility study reports.
Stability	YES ☑ NO ☐	The elastomer of the primary medicinal powder container is changed. Therefore, component stability needs to be evaluated as well as the leachable profile on stability.	Design verification plan, aging stability data to accept new component/material.	Design verification plan, test protocols and report, design verification summary report.
Drug delivery system/medicinal product compatibility	YES ☑ NO ☐	The elastomer of the medicinal powder container is changed which could change the extractables and leachables profile and as such the medicinal product quality/shelf-life.	Conduct extractable assessments on the new elastomer.	Material extractable study reports. Stability reports.
Processes	YES ☑ NO ☐	The elastomer of the medicinal powder container is changed which could impact the moulding capability of the component. There would be a requirement to demonstrate the component is unchanged and meets the component specification, with consideration if further assembly process validation is required.	Demonstrate the component from new material meets the current component specification. Perform assembly process validation assessments as necessary.	Component moulding process validation report. Assembly process validation report.
Software	YES ☐ NO ☑	No software involved.	Not applicable.	Not applicable.
Usability	YES ☐ NO ☑	No user interface change.	Not applicable.	Not applicable.

Table B.8 *(continued)*

Impact of change, planning and execution of activities				
Clinical data set	YES ☑ NO ☐	Aerosol performance and therefore bioavailability could be impacted by the change.	Aerosol performance comparison studies review from design verification.	Decision on impact of any aerosol performance change.
Regulatory compliance	YES ☑ NO ☐	Materials contact the medicinal product are affected, therefore preparation for regulatory update is needed.	Conclude regulatory pathway for making the update.	Pathway agreed and prepared.

Table B.9 — Completed template for a final evaluation of a primary container material change in a dry powder inhaler

Phase C — Final evaluation
6. Review data Impacted? YES ☑ NO ☐ Rationale: All moulding, assembly and process studies for the elastomer change passed and demonstrated equivalent performance with the original material. Biocompatibility, leachables and extractables of the material were also confirmed as acceptable. Design verification confirmed the stability and basic performance of the dry powder inhaler. However, a small change in the aerosol profile was noted.
7. Evaluate clinical comparability *Instructions: Determine the impact to the existing clinical data set using the list given in 4.2.3 and determine whether there are gaps in the available data to support the clinical safety and efficacy of the modified finished product.* Is clinical bridging required? YES ☑ NO ☐ Rationale: The small change in the aerosol profile as a result of the elastomer change was evaluated against the clinical data set which could impact bioavailability of the medicinal product. Recommend further pk/pd bioavailability study based on particle distribution profile.
8. Decision to proceed with change Proceed with change? YES ☑ NO ☐ Rationale: Change can proceed once clinical bridging is confirmed. There are no other constraints to the change being made. *Instructions: Any reporting or submission activities needed to obtain authorization from the competent authority should be performed in accordance with applicable statutory and regulatory requirements prior to implementation of the change.*

B.4 Example for assessing a medicinal product formulation change

This clause provides an example of completed templates for assessing, evaluating and documenting changes to the drug delivery system, necessitated by changes to the medicinal product.

This example (see Tables B.10 to B.12) and the conclusions provided are purely hypothetical and should not be interpreted to obviate the critical interactions between sponsors and regulators, who ultimately determine whether clinical data is required to support the proposed change.

Table B.10 — Completed template for defining, identifying and assessing a medicinal product formulation change for a pre-filled autoinjector

Name of Change: Medicinal product formulation change for a pre-filled autoinjector (Change Reference xxxx)
Phase A — Define and assess
1. Define change A monoclonal antibody medicinal product is currently licensed in a disposable pre-filled autoinjector presentation. Feedback has been received from patients using the product that they experience pain upon injection. As a means to improve the comfort of the injection, the manufacturer is introducing a modified formulation at pH 7,5. The current formulation is pH 5,5. Other than a change in buffer, no other changes have been made to the formulation. Changing the pH increased the viscosity of the medicinal product from 2,1 cP to 3.4 cP. The following aspects of the pre-filled autoinjector are NOT changing: — intended use, indication, and route of administration;