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Cardiovascular implants and extracorporeal systems — Vascular device-drug combination products —

Part 2: Local regulatory information

Implants cardiovasculaires et circuits extra-corporels — Produits de combinaison médicament-dispositif vasculaire —

Partie 2: Directives règlementaires locales

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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).

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 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*.

This second edition cancels and replaces the first edition (ISO/TR 12417-2:2017), which has been technically revised.

The main changes are: editorial changes have been made regarding the use of requirements, recommendations, permissions and possibilities.

A list of all parts in the ISO 12417 series can be found on the ISO website.

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 was prepared in order to provide local regulatory information for vascular device-drug combination products (VDDCPs).

VDDCPs are medical devices with various clinical indications for use in the human vascular blood system. A VDDCP incorporates, as an integral part, substance(s) which, if in final formulation separately, can be considered to be a medicinal product (drug product) but the action of the medicinal substance is ancillary to that of the device and supports the primary mode of action of the device.

Only regulatory issues related to drug(s) combined with the vascular device based on the ancillary function of the VDDCP are covered by this document.

Although this document attempts to represent the state-of-the-art regarding regulatory requirements for pre and post-approval changes, these requirements are evolving and as such, it is strongly suggested that the applicant consult with the regulatory authority under which whose jurisdiction the VDDCP falls. This is most easily done by accessing the local authorities' current webpage.

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

NOTE 1 For issues related to the primary mode of action of the vascular device, the reader can find it useful to consider a number of other International Standards given in the Bibliography.

NOTE 2 Potential clinical events are defined in ISO 12417-1:2015, Annex A.

Cardiovascular implants and extracorporeal systems — Vascular device-drug combination products —

Part 2: Local regulatory information

1 Scope

This document provides region-specific information for:

— local submissions and approvals for vascular device-drug combination products (VDDCPs) in countries and regions around the world;

— changes related to the drug-containing part and how they are evaluated by different local regions.

For implanted products, this document is considered as a supplement to ISO 14630, which specifies general requirements for the performance of non-active surgical implants.

This document is considered also as a supplement to ISO 12417-1, and any relevant device-specific standards, such as the ISO 25539 series specifying requirements for endovascular devices. This document also addresses VDDCPs that are not necessarily permanent implants.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 12417-1, *Cardiovascular implants and extracorporeal systems — Vascular device-drug combination products — Part 1: General requirements*

ISO 14630, *Non-active surgical implants — General requirements*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 12417-1, ISO 14630 and the following apply.

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

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

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

3.1
active pharmaceutical ingredient
API
drug substance
pharmacologically active (drug or medicinal) substance used as a raw material, which is coated on, bound to or incorporated into the device to achieve an ancillary device function, such as minimizing vascular restenosis

3.2
batch
quantity of VDDCP at the final stage or pre-final stage of manufacture which has undergone the same manufacturing cycle, using the same components (e.g. same coating solution, same device size), and meets the same specifications

3.3
change
alteration to an activity or to the VDDCP to improve or to maintain the composition or performance of a VDDCP

Note 1 to entry: This term includes small alterations to a VDDCP, a manufacturing process or a test procedure, even if it is not necessarily captured by a corrective action/preventative action (CAPA) system, and can require reporting to local regional authorities.

3.4
clinical event
complication, failure or device-related observation that can be observed with clinical use of a VDDCP

Note 1 to entry: Such events can possibly not have clinical significance and can possibly not be attributable to the VDDCP.

3.5
critical component
component whose specifications, if not met, can result in unacceptable risk to the patient, clinician or others, or can have a significant impact on performance

3.6
device part of the VDDCP
DP
part of the VDDCP intended to treat vascular disease by temporary or long-term intervention or implantation that does not achieve its PMOA in or on the human body by pharmacological, immunological, or metabolic means, but can be assisted in its function by such means

3.7
drug product
medicinal product
API, in its final form for administration to the patient (e.g. tablet, solution, spray), that is intended to prevent, diagnose or treat disease, and that achieves its principal intended action in or on the body by pharmacological, immunological or metabolic means

3.8
drug-containing part of the VDDCP
DCP
part of the VDDCP that consists of the active pharmaceutical ingredient or matrix and associated device interfaces intended to assist in the primary mode of action of the device and/or diminish or ameliorate an unintended effect that placement of the device part can stimulate

Note 1 to entry: Some VDDCPs can have an incorporated medicinal or drug substance primarily intended to optimize the DP properties of the VDDCP.

3.9
drug-containing part interface
DCP interface
interface between the matrix containing the API and packaging materials with direct DCP contact or device surface(s), or interface between the matrix and the API

3.10
drug content
total labelled amount of active pharmaceutical ingredient in a VDDCP

Note 1 to entry: Drug content can be expressed as µg/DCP of a certain size.

3.11
drug delivery
local interaction between the VDDCP drug and the in vivo environment, whether the drug is released from, eluted from or remains bound to the VDDCP

3.12
drug release profile
in vitro characterization of the active pharmaceutical ingredient released from the DCP of a VDDCP over time

Note 1 to entry: For example, the drug release can be characterized by a drug elution test and can include either a curve shape (or profile) or a drug release rate, or both.

3.13
efficacy
ability of the VDDCP to achieve the planned and desired physiological result

3.14
evaluate
appraise or analyse qualitatively

3.15
excipient
additional material, other than the API, that are intentional components of the drug-containing part of a VDDCP

EXAMPLE Filler, extender, diluent, wetting agent, solvent, colorant, stabilizer, antioxidant, preservative, pH maintainer, polymers, adhesives.

3.16
functionality
ability of the VDDCP to perform either physically, chemically or mechanically, or all, as designed

Note 1 to entry: Functionality does not include the physiological response to the VDDCP (i.e. efficacy).

3.17
matrix
organic or inorganic material, other than living cells, intentionally applied by a manufacturer to a vascular device and designed for the purpose of drug storage, local drug activity at the surface and/or enabling, retarding, delaying or modifying drug release

Note 1 to entry: The matrix can be permanent or temporary (dissolvable, absorbable or degradable), include surface treatments such as primers, be a coating with or without an active pharmaceutical ingredient, or consist of multiple excipients and/or multiple active pharmaceutical ingredients.

3.18
mode of action
means by which a product achieves an intended therapeutic effect or action

Note 1 to entry: This can be a primary or ancillary mode of action.

3.19
pharmacokinetics
absorption, distribution, metabolism and elimination of a drug in vivo

3.20
primary mode of action
single mode of action of a combination product that provides the most important therapeutic action of the combination product

Note 1 to entry: The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product

Note 2 to entry: Additional guidance on the drug-related aspects of the drug-containing part of the VDDCP can be found in International Conference on Harmonization Guideline IC H Q1A[29].

3.21
uniformity of drug content
comparison of the uniformity of the drug content between individual VDDCPs within each batch as compared to the labelled claim

3.22
vascular device-drug combination product
VDDCP
vascular medical device that incorporates one or more APIs as an integral part (ancillary mode of action) to that of the device, but not necessarily to the VDDCP PMOA

Note 1 to entry: The VDDCP can be permanently deployed (i.e. it can be an implant like a drug-eluting stent) or temporarily deployed (i.e. it can be a drug-eluting balloon).

3.23
vascular device-drug combination product specification
VDDCP specification
required list of test procedures and appropriate acceptance criteria which are numerical limits, ranges or other criteria for the tests described

Note 1 to entry: A specification is a critical quality standard. It establishes the set of criteria to which a VDDCP has to conform.

Note 2 to entry: Additional guidance on the drug-related aspects of the drug-containing part of the VDDCP can be found in International Conference on Harmonization Guideline IC H Q6A[37].

4 Information on device- and drug-related aspects — Applicable documents for local guidance

4.1 General

The following region-specific information identifies the regional regulatory authorities responsible for VDDCPs and provides general clinical evaluation and audit requirements for VDDCPs.

NOTE 1 Region-specific requirements can deviate from harmonized International Standards.

NOTE 2 At the publication of this document, the following information is believed to be accurate and can change over time. Current guidance can be directly obtained from the regulatory authorities in the region of interest.

4.2 Australia

4.2.1 General

VDDCPs are approved by the department of health through the Therapeutic Goods Administration (TGA).

NOTE For more information, see the Therapeutics Goods Administration website and for Australian regulatory guidelines for medical devices, see Reference [136].

4.2.2 Australia: Managing changes

See the website of the local authority above for the responsibilities of deciding whether a submission or change notification is subject to requirements.

It is the responsibility of the manufacturer to decide if a submission or change notification is subject to requirements. This information is then communicated to the TGA by the Australian sponsor.

See also Table 2 for managing changes that can impact the DCP.

4.2.3 Australia: Clinical evaluation requirements

VDDCPs are subject to requirements for a clinical study (but it need not be a local study). If the study is conducted in Australia, an exemption is granted by TGA prior to initiation of the study which allows products not included on the Australian Register of Therapeutic Goods to be supplied as part of the clinical trial.

NOTE The TGA has two pathways in Australia for clinical trials – Clinical Trial Notification (CTN) which involves a notification to the TGA and Clinical Trial Exemption (CTX) which requires a formal approval from the TGA. The CTX is generally for studies where the experimental device introduces a new technology, a new material or a new concept or for trials that are considered high risk.

4.2.4 Australia: Audit requirements

An appropriate quality system audit can be required prior to market approval.

NOTE For more information, see ARGMD[81] on the Therapeutics Goods Administration website.

4.3 Brazil

4.3.1 Brazil: Managing changes

VDDCPs are approved by the National Health Surveillance Agency (ANVISA). In Brazil, medical devices are regulated by

a) the national law "Lei 6360/1976" which regulates drugs, medical devices, cosmetics and other sanitary products,

b) the decree "Decreto 79094/1977" which regulates the law "Lei 6360/1976" and the ANVISA Board Collegiate Resolutions,

   — RDC 185/2001 for the Registration, post-market changes, revalidation and cancellation of registration of medical devices in the Brazilian Health Surveillance Agency;

   — RDC 14/2011 for Establishing the technical regulations with requirements for grouping of medical device.

NOTE For more information, see the ANVISA website.

ANVISA expects that APIs are in compliance with the Brazilian Pharmacopoeia (or other specified compendia).

The pharmaceutical products, medicines and other products subject to sanitary surveillance are expected to meet the standards and specifications established in the Brazilian Pharmacopoeia (see ANVISA website).

In the absence of an official Brazilian monograph, the use of a foreign official monograph is allowed.

See website of the local authority above for the responsibilities of deciding whether a submission or change notification is subject to requirements.

See also Table 2 for managing changes that can impact the DCP.

4.3.2 Brazil: Clinical evaluation requirements

VDDCPs are subject to requirements for a clinical study (but it need not be a local study) according RDC 56/2001. If the study is conducted in Brazil, the clinical study protocol needs to be approved, prior to initiation of the study, by ANVISA according RDC 39/2008. The final report for the study primary end point(s) is completed prior to submission to ANVISA.

4.3.3 Brazil: Audit requirements

A manufacturing audit is subject to requirements prior to market approval. The manufacturing site is certified under RDC 59/2000 (Brazil quality system requirement) prior to submitting the product to ANVISA for registration. An audit can be required prior to market approval if the product is not within the current scope of the corresponding quality assurance system approval certificate.

The manufacturing RDC 59/2000 certificate or ISO 13485 MDSAP certificate is presented together with the submission dossier.

4.4 Canada

4.4.1 Canada: Managing changes

VDDCPs are approved by Health Canada.

NOTE For more information, refer to the Health Canada website[137].

See the website of the local authority given above for the responsibilities of deciding whether a submission or change notification is subject to requirements.

It is the responsibility of the Health Canada to decide if a submission or change notification is subject to requirements based on information provided by the manufacturer.

See also Table 2 for managing changes that can impact the DCP.

4.4.2 Canada: Clinical evaluation requirements

VDDCPs are subject to requirements for a clinical study (but it need not be a local study). It is suggested that a pre-CTA submission be scheduled with Health Canada (see website for Pre-CTA details). If the study is conducted in Canada, the clinical study protocol needs to be approved by Health Canada prior to initiation of the study per the Clinical Trial Application (CTA) process (see Health Canada website for more information of the CTA process).

4.4.3 Canada: Audit requirements

An audit can be required prior to market approval if the product is not within the current scope of the corresponding quality assurance system approval certificate.

4.5 European Union (EU)

4.5.1 EU: Managing changes

VDDCPs are assessed for conformity by a Notified Body before approval as medical devices according to Medical Device Regulation (EU) 2017/745. The Notified Body seeks a scientific opinion or consultation from one of the competent authorities (national regulatory authorities designated by member states) or the European Medicines Agency and from an Expert Panel review ((56) of Regulation (EU) 2017/745.). MEDDEV 2.1/3 is a guideline explaining the consultation process for VDDCPs as well as the necessary documentation to be provided for consultation.

Per the European Pharmacopoeia (EP), APIs follow the API monograph if one exists. If APIs are imported, then the authenticity of API GMP status can be verified per the Falsified Medicines Directive 2011/62.

NOTE 1 The Notified Bodies, competent authorities, and more information on the EU regulatory framework is contained within Reference [138].

NOTE 2 MEDDEV 2.1/3-related information can be found in Reference [138].

The NB-MED is an organization of the Notified Bodies that published a guidance document (NB-MED/2.5.2 /rec2) which comprises recommendations accepted by the European Forum of Notified Bodies Medical Devices (NB-MED). Although they set out information on matters relating to the directives, this information is for guidance only, to help the user to meet their obligations, whether the user is a manufacturer, a Notified Body or an interested party.

It is the responsibility of the Notified Body to decide if a submission or change notification is subject to requirements, based on information provided by the manufacturer.

NOTE 3 MEDDEV 2.1/3, Borderline products, drug delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative.

See also Table 2 for examples of how to manage changes that can impact the DCP.

4.5.2 EU: Material inclusion and labelling requirements

Under the conformity assessment procedures per Annex I, General Safety and Performance Requirements (GSPR)s, justification and updates to the technical documentation can be required for the inclusion of materials, chemicals, or substances deemed to be potential hazardous to patients, users, and/or the environment. Per Annex I GSPRs, labelling of medical devices can require additional patient and user notifications to comply with regional requirements.

4.5.3 EU: Clinical evaluation requirements

VDDCPs are subject to requirements for a clinical evaluation as given in European Union medical device regulations. A clinical study is performed unless it is duly justified to rely on existing clinical data.

Prior to submission of a clinical evaluation that includes a clinical study, it is possible that the study design can be discussed with the relevant Notified Body and the drug consultation body.

If a study is needed, there are country-specific requirements. The approval of clinical studies applications in the EU is the responsibility of the individual Member States (see Reference [138]).

4.5.4 EU: Audit requirements

An audit can be required prior to market approval if the product is not within the current scope of the corresponding quality assurance system approval certificate.

For Class III VDDCPs incorporating as an integral part an API, conformity assessment is performed.

4.6 India

4.6.1 India: Managing changes

VDDCPs are approved by the Drugs Controller General of India (DCGI) and are governed by The Drugs and Cosmetic Act 1940 and rules 1945.

NOTE For more information, see Reference [139] for the responsibilities of deciding whether a submission or change notification is subject to requirements.

4.6.2 India: Clinical evaluation requirements

VDDCPs are subject to requirements for a local clinical study. The clinical study protocol needs to be approved prior to initiation of the study. The final report for the study primary end point(s) is completed prior to submission for approval.

4.6.3 India: Audit requirements

A manufacturing audit can be required prior to market approval.

4.7 Japan

4.7.1 Japan: Managing changes

VDDCPs are Class IV devices and are approved by the Minister of Health, Labour and Welfare (MHLW) as medical devices.

The application for approval of VDDCPs is submitted to Pharmaceuticals and Medical Devices Agency (PMDA).

NOTE 1 For more information, see Reference [140].

VDDCPs are subject to requirements for applicable local approval.

NOTE 2 See also the Bibliography for local guidelines.

See website of the local authority above for the responsibilities of deciding whether a submission or change notification is subject to requirements.

See also Table 2 for examples of how to manage changes that can impact the DCP.

4.7.2 Japan: Clinical evaluation requirements

VDDCPs are subject to requirements for a clinical study. A consultation with PMDA helps to determine if already existing international data is sufficient, or if some additional data is needed to be collected locally. Clinical Trial Notification (CTN) needs to be submitted to PMDA prior to initiation of the study. In the case of the first trial for the device in Japan, the clinical study protocol and investigator's brochure are submitted with the CTN and endorsed by MHLW/PMDA from a safety and ethics point of view. The final report for the study primary end point(s) is completed prior to submission of the marketing application to PMDA.

NOTE See Reference [158] on Good Clinical Practice for Medical Devices (GCP).

4.7.3 Japan: Audit requirements

A manufacturing audit can be required prior to market approval.

4.8 People's Republic of China (PRC)

4.8.1 PRC: Managing changes

VDDCPs are approved by the National Medical Products Administration of China (NMPA) (formerly CFDA, State FDA or SFDA).

VDDCPs are subject to requirements for applicable GB National Standards and YY medical industrial standards (see Table 1 for codes).

VDDCPs without country of origin approval cannot be submitted to NMPA. In addition, the API is also to have country of origin approval or need to have been approved by NMPA prior to submission to NMPA.

NOTE 1 Table 1 gives an overview of regional-standard codes and abbreviations.

Table 1 — Chinese standard codes and abbreviations

Code	Type of standard	Institution
GB	Mandatory national standard	SAC
GB/T	Recommended national standard	SAC
GB/Z	National standardization, technical document	SAC
YY	Mandatory medical industrial standard	NMPA
YY/T	Recommended medical industrial standard	NMPA
Key		
SAC: Standardization Administration of China		
NMPA: China Food and Drug Administration		

NOTE 2 For more information, see the NMPA website for general information on device registration[141].

NOTE 3 Refer also the Bibliography for local guidelines.

See the website of the local authority above for the responsibilities of deciding whether a submission or change notification is subject to requirements.

See also Table 2 for managing changes that can impact the DCP.

NOTE 4 The term of validity of the Medical Device License is 5 years according to the new NMPA regulation. NMPA Regulation for the Supervision and Administration of Medical device (No. 739 Order) can be found (in Chinese language) in Reference [141] and NMPA Provision of Administration for Medical Device Registration (Regulation #4) can be found (in Chinese language) in Reference [142].

According to Order #739 if a substantial change of the design, raw materials, manufacturing process, intended use, forms of operation, etc. for Class II and Class III medical devices that are already registered, and those changes can possibly affect the safety and effectiveness or efficacy of medical devices, the registration applicant submits a change application to the original registration authority. If a non-substantial change occurs that will not affect the safety and effectiveness of the medical devices, the registration applicant files the change on record with the original registration authority.

According to the Regulation #4, in case of any changes to the content of the Medical Device license for a Class II and Class III Medical Device and its Annexes (e.g. product technical requirement), the applicant submits the application to the original authority for the changes and submits the documents according to the appropriate requirements.

— For changing the product name, model, specification, structure and components, intended use/ indication, product technical requirement, manufacturing site of import medical devices etc., these are change of permission items (CP), the applicant submits the application and relevant documents to the original regulatory authority for approval.

— For changing the name and/or domicile of the applicant or changing the name and/or the domicile of the deputy agent, these are change of registration items (CR), the applicant submits the application and relevant documents to the original regulatory authority for approval of the changes. For changing the manufacturing site address of a China domestic medical device on the medical device license, the applicant submits the application and relevant documents to the original regulatory authority after the manufacturing site is approved.

4.8.2 PRC: Clinical evaluation requirements

VDDCPs are subject to requirements for a clinical evaluation or a clinical study.

NMPA Provisions of medical device clinical trials No. 5 regulation can be found (in Chinese language) in Reference [143] where both non-drug elution and drug elution devices are discussed.

NOTE 1 Further guidance for the regulatory requirements for the conduct of a clinical trial is provided in the document "Regulations for the Supervision and Administration of Medical Devices (Order #739)" in Reference [141] (in Chinese language).

NOTE 2 For further guidance on the technical requirements for a clinical study for a coronary drug-eluting stent refer to "Notification on guidance for coronary drug-eluting stent clinical trial" in Reference [144] (in Chinese language).

4.8.3 PRC: Audit requirements

A manufacturing audit is subject to requirements prior to market approval. There are several scenarios. For imported medical device of Class III implanted device, NMPA have the right to audit the manufacturer at any time. It can be possible to invite NMPA's officials to inspect the quality system.

NOTE For general information, please see website of the local authority above for the responsibilities of deciding whether a submission or change notification is subject to requirements.

4.9 Russia

4.9.1 Russia: Managing changes

Russian regulations are rapidly evolving with documents from the EurAsian economic commission coming into force in 2016. Review of current Russian regulations is not informative at this time and for these reasons Russian regulatory information is not present in Table 2. Please refer to currently available digital resources for confirmation of the requirements.

NOTE 1 The Federal Service for Control in Healthcare is the approving state registration for medical devices. The Federal Service for Control in Healthcare reports to the Ministry of Health.

NOTE 2 Manufacturers of VDDCPs issue a declaration of conformity (GOST R) that is submitted for certification body review and registration in the state database.

NOTE 3 APIs are in compliance with the Russian Pharmacopoeia.

4.9.2 Russia: Clinical evaluation requirements

VDDCPs are subject to requirements for a summary of available clinical data. If a study is conducted in Russia, the clinical study protocol needs to be approved prior to initiation of the study. The final report for the study primary end point(s) is completed prior to submission.

4.9.3 Russia: Audit requirements

A manufacturing audit is not required prior to market approval in all cases, for imported VDDCPs.

4.10 United States of America (USA)

4.10.1 USA: Managing changes

VDDCPs are approved or determined to be substantially equivalent to a marketed device and cleared for market by the US Food and Drug Administration (FDA). For VDDCPs in which the primary mode of action is from the device (e.g. stents and balloons), FDA's Center for Devices and Radiological Health (CDRH) has primary review responsibility and consults with the Center for Drug Evaluation and Research (CDER) regarding drug-related issues. For VDDCP, early interaction with FDA is suggested. Information on the USFDA presubmission process can be found in Reference [145].

NOTE 1 Information on general FDA policies and procedures can be found in Reference [146].

NOTE 2 Information on FDA review of combination products can be found in Reference [147].

NOTE 3 There are many FDA guidance documents applicable to submissions for VDDCPs. These guidance documents can be found in Reference [148].

If APIs are in compliance with the United States Pharmacopoeia (USP), this is noted in submissions to the FDA.

NOTE 4 Refer also to the Bibliography for local guidelines.

It is the responsibility of the manufacturer to decide if a submission or change notification is subject to requirements, using guidance from the USFDA website. The USFDA determines if the selected approach is appropriate or if additional submissions are needed.

See website of the local authority above for the responsibilities of deciding whether a submission or change notification is subject to requirements.

Additionally, it can be helpful to see the following USFDA Guidance documents given in Reference [149].

NOTE 1 Changes or modifications during the conduct of a clinical investigation are given in Reference [149].

NOTE 2 Refer to Reference [150] when deciding when to submit a 510(K) for a change to an existing device (K97–1).

NOTE 3 Refer to Reference [151] for Guidance for industry and FDA staff: modification to devices subject to pre-market approval (PMA), the PMA supplement decision making process.

NOTE 4 Refer to Reference [152] for Guidance for industry and FDA staff: submissions for postapproval modifications to a combination product approved under a BLA, NDA, or PMA.

NOTE 5 Refer to Reference [153] for Guidance for industry: changes to an approved NDA or ANDA.

NOTE 6 Refer to Reference [154] for Guidance for industry: changes to an approved NDA or ANDA – questions and answers.

NOTE 7 Refer to Reference [155] for Guidance for industry: CMC postapproval manufacturing changes to be documented in annual reports.

NOTE 8 Refer to Reference [157] for Guidance for industry: scale-up and postapproval changes: chemistry, manufacturing, and controls, in vitro dissolution testing, and in vivo bioequivalence documentation.

NOTE 9 It is suggested to consult the USFDA website for: 30-Day Notices, 135-Day premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes[156]. See also Table 2 for managing changes that can impact the DCP.

4.10.2 USA: Clinical evaluation requirements

VDDCPs are subject to requirements for clinical data (but studies need not always be entirely local, if data can be generalizable to the US patient population). If a study is conducted in the USA, the clinical study protocol needs to be approved by the USFDA prior to initiation of the study. If the study is conducted outside the USA, the pre-submission process can be used to determine if the study as designed is likely to support a marketing application in the USA. The final report for the study primary end point(s) is completed prior to submission of a marketing application to the USFDA. In addition to the primary end point data, all available follow-up data are included at the time of the marketing application per 21 CFR 814.20 (b)(6)(ii) and (b)(8)(ii).

4.10.3 USA: Audit requirements

Inspections of the API and VDDCP manufacturing and/or testing sites as well as the clinical study sites can be required prior to market approval.

5 Managing changes that can impact the DCP

5.1 General

Clause 5 provides examples of the types of evaluations that can be considered for specific types of changes that can impact the API and/or DCP (e.g. VDDCP specifications, manufacturing, test methods, packaging), and whether these types of changes can require additional review by regulatory authorities.

NOTE Review requirements/laws can change over time, so the consultation of appropriate regulatory bodies in all countries where the VDDCP is under consideration for marketing authorization or is already approved is suggested. The same process for evaluating changes can be adopted whether the VDDCP is under consideration or approved, but the reporting requirements can be different.

The manufacturer determines and demonstrates that following any change(s), the final product remains safe and effective and meets already established or new performance criteria.

5.2 Change evaluation

If there are any changes in the design or manufacture of the DP or DCP (pre- or post-market) which can have an effect on the quality, safety or usefulness of the API in the VDDCP, it is possible that the changes in response to clinical events or otherwise, require approval prior to implementation in a clinical study and/or for marketing. Change(s) can be evaluated using a change control system as outlined in quality system standards and regulatory requirements where the VDDCP are sold.

For example, ISO 13485 and ISO 14971:2019 can apply.

5.2.1 Identify changes

The manufacturer can identify and document specific changes to the VDDCP specifications, manufacturing, test methods and packaging that can impact the API and/or DCP. See also 5.2.2 and 5.3.

Examples of specification changes include:

a) change(s) to the drug content, impurities, drug release/pharmacokinetics, or uniformity of drug content (i.e. content uniformity), at batch release and over the shelf life of the DCP;

b) change(s) to the shelf life of the VDDCP;

c) change(s) to the retest date of the API (e.g. extend or reduce expiry date for raw material API);

d) change(s) to the DCP formulation.

NOTE 1 A change in the API is considered a new product.

NOTE 2 Specifications can be tightened, widened or changed altogether.

The list below is not an all-inclusive list.

Examples of manufacturing changes are:

a) change(s) to supplier(s) of DCP components:

   — supplier of a critical component (e.g. API, matrix, solvent);

   — supplier of a non-critical component (e.g. alcohol or sterile water) that does not come in direct contact with the DCP;

b) change(s) to the manufacturing site for the DCP or VDDCP;

   NOTE Change(s) to the DP that can affect the DCP or DCP interface can also be considered. For example, a change to the metal stent surface processing site can affect the ability of a polymer interface coating to adhere, and ultimately can affect the DCP properties.

c) change(s) to manufacturing methods for the DCP or VDDCP such as process container material or volume changes for the API-containing solution;

d) change(s) to process technology such as spray versus dip coating;

e) change(s) to sterilization process.

The list below is not an all-inclusive list.

Examples of test methods changes include:

a) replacement or elimination of a test method (e.g. UV-vis versus NMR for drug release profile testing, or removal of a residual solvents test);

b) change(s) to testing frequency or sample size (e.g. for stability tests or for batch release);

c) modifications or refinement types of change(s) to testing procedures (e.g. add sample conditioning such as simulated-use prior to particulate testing.

The list below is not an all-inclusive list.

Examples for packaging changes include:

a) change(s) to a component of the packaging system that is in contact with DCP, or can influence DCP, such as changes to a protective tubing, sterile barrier, or a foil pouch to prevent light, or elimination of an inner pouch;

b) change(s) to packaging methods that can influence DCP or VDDCP stability, such as the sealing process;

c) change(s) in storage conditions, such as storage at 5 °C ± 3 °C versus 25 °C at a 60 % relative humidity (RH) versus 30 °C at a 75 % RH.

NOTE 3 See ISO 11607-1 for additional information for packaging.

The above types of changes have been incorporated into Table 2, as examples of changes that can have different regulatory submission requirements, depending on the region where the application is being made.

5.2.2 Risk evaluation

Whenever changes are made in materials, construction, configuration, application or processing methods, an appropriate analysis of the potential impact of the change on the failure modes and performance or functionality of the VDDCP can be conducted. Appropriate testing can be conducted as deemed necessary (some examples are presented in Table 2).

For more information, ISO 14971 can be consulted during the evaluation of risk process.

5.2.3 Guidance for change evaluation

Whenever changes are determined to have a potential impact on failure modes and/or performance of the VDDCP, the following tools can be appropriate for managing the effects of a change:

For supplier changes:

— For a new supplier of a VDDCP component, supplier agreements that are put in place can require suppliers to inform the VDDCP manufacturer of any impending changes such as changes in formulation specifications or manufacturing processes.

— If an existing supplier of a VDDCP component makes or plans to make a change:

  — the manufacturer of a VDDCP can choose to request documentation (such as validation testing) to confirm compliance to applicable specifications prior to implementation of the change if possible;

  — consider performing confirmatory testing on the incoming component of the DCP or VDDCP.

For internal changes:

— change control activities such as routine review and update of standard operating procedures (SOPs) can be sufficient;

— for training changes, such as training and retraining activities, documentation can be sufficient;

— additional verification/validation testing can be necessary.

5.2.4 Pre-market

If a manufacturer makes changes that can influence the DCP while the VDDCP is under consideration by the local regulatory authority, the regulatory authority can be contacted to assess whether these changes need to be submitted.

NOTE In some regulatory regions (e.g. USFDA), changes can be reported (via formal submission or via email).

5.3 Interactions with region-specific regulatory authorities — Post-commercialization

If changes are made, there can be different regional regulatory requirements for pre-approval, notification, or documentation prior to change implementation, depending on where the product is in development or commercialization.

The information in Table 2, intended for guidance, was developed at the time this document was written and can become outdated therefore it is not to be considered as prescriptive or exhaustive.

The regulatory environment for VDDCPs is evolving. The following information is intended to provide an awareness of the types of submissions that can be appropriate across regional regulatory authorities. Checking with the appropriate region-specific regulatory authorities for post-commercialization changes will ensure that this information is still valid.

NOTE If a VDDCP manufacturer makes multiple changes, the type and degree of risk (see also 4.2.2) can change, as well as the way the changes are evaluated. In addition, consideration can be given to whether a single or multiple submissions are needed, and the related submission type(s).

Table 2 — Example of region-specific change information for regional regulatory authorities by country

Change	Australia (TGA)	Brazil (ANVISA)	China (NMPA)	EU (NB)	Japan (PMDA)	US (FDA)
Types of change per country	SC = Substantial change; requires approval MC = Minor change; no approval needed prior to implementation, supporting evidence can be audited by the TGA at periodic inspection	CN = Change notification (requires approval) N = Notification; no approval needed to be implemented	CP = Change to permission items (prior approval is subject to requirements) CR = Change to register items; prior approval is subject to requirements	NB = Notified body RN = (no approval needed prior to implementation) NCA = national competent authority CN = change notification; requires approval	PCA = Partial change application (requires approval)	30DN = 30d Notice 180DS = 180d PMA supplement 180PT = Panel track PMA supplement AR = PMA annual report PMA = Original PMA RT = Real time PMA supplement SPEC = Special PMA supplement
Drug content: Change labelled amount	Type 1: SC (D, B, IVP[a], C[a])	Type 1: CN (D, B, IVP[a] C[a])	Type 1: CP (D, B, IVP,C[a])	Type 1: CN (NB w/NCA) (D, B, IVP[a],C[a])	Type 1: PCA (D, B, IVP[a], C[a])	Type 1: 180DS (D, B, IVP[a], C[a])
Drug content: Widen tolerances	Type 1: SC (D, B, IVP[a], C[a])	CN (D, B, IVP[a], C[a])	Type 1: CP (D, B, IVP, C[a])	Type 1: CN (NB w/NCA) (D, B, IVP[a], C[a])	Type1: PCA (D, B, IVP[a], C[a])	180DS (D, B, IVP[a], C[a])
Drug content: Tighten tolerance	Type 2: MC (D, B[a])	Type 1: N (D)	Type 1: CP (D, B, IVP)	No submission (D)	Type 1: PCA (D, B, IVP[a], C[a])	Type 2: AR – historic data (D, B[a]) Type 1: RT/180DS – CAPA (D, B[a])
Impurities: Increase total or single	Type 1: SC (D,B,IVP[a])	Type 1: CN (D, B, IVP[a])	Type 1: CP (D, B, IVP)	Type 1:CN (NB w/NCA[a]) (D, B, IVP[a])	Type 1: PCA (D, B, IVP[a])	Type 1: 180DS (D, B, IVP[a])
Impurities: Decrease total or single	Type 2: MC (D, B)	Type 1: N (D)	Type 1: CP (D, B, IVP)	RN (D, B[a])	Type 1: PCA (D, B, IVP[a])	Type 2: AR – historic data (D, B[a]) Type 1: 180DS – CAPA (D, B[a])
Drug release profile: Change specified curve	Type 1: SC (D, B, IVP[a], C[a])	Type 1: CN (D, B, IVP[a], C[a])	Type 1: CP (D, B, IVP, C[a])	Type 1: CN (NB w/NCA) (D, B, IVP[a], C[a])	Type1: PCA (D, B, IVP[a],C[a])	Type 1: 180DS (D, B, IVP[a], C[a])

Key

D : documentation

B : bench testing (can include engineering, or in vitro or in vivo biocompatibility)

IVP : in vivo preclinical (can include IVIVC)

C : clinical

Type 1: notification and acceptance by the regulatory authority prior to change implementation

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Drug release profile: Widen tolerance	Type 1: SC (D, B, IVP[a], C[a])	Type 1: CN (D, B, IVP[a], C[a])	Type 1: CP (D, B, IVP)	Type 1: CN (NB w/NCA)	Type 1: PCA (D, B, IVP[a], C[a])	Type 1: 180DS (D, B, IVP[a], C[a])
Drug release profile: Tighten tolerance	Type 2: MC (D, B[a])	Type 1: CN (D, B[a])	Type 1: CP (D, B, IVP)	No submission (D, B[a])	Type 1: PCA (D, B, IVP[a], C[a])	Type 2: AR – historic data (D, B[a]) Type 1: RT/180DS – CAPA (D, B[a])
Content uniformity: (batch release test) Widening tolerance	Type 1: SC If no pharmacopeia: (D, B, IVP[a], C[a])	Type 1: If no pharmacopeia: CN (D, B, IVP[a], C[a])	Type 1: CP (D, B, IVP[a])	Type 1: If no pharmacopeia: CN (NB w/NCA) (D, B, IVP[a], C[a])	Type 1: If no pharmacopeia: PCA (D, B, IVP[a], C[a])	Type 1: 180DS (D, B, IVP[a], C[a])
Content uniformity: Tightening tolerance	Type 2: MC (D, B[a])	Type 1: N (D, B[a])	Type 1: CP[a] (D, B)	No submission (D, B[a])	Type 1: PCA (D, B, IVP[a], C[a])	Type 2: AR – historic data (D, B[a]) Type 1: RT/180DS – CAPA (D, B[a])
Shelf life of the VDDCP Reduce	Type 1: SC (D, B)	Type 1: CN (D, B)	Type 1: CP (D, B)	Type 1: CN (NB only) (D, B)	Type 1/Type 3: PCA / Consult (D, B),	Type 2: 180DS (D, B)

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Shelf life of the VDDCP Extend date	Type 1: SC (D, B)	Type 1: CN (D, B)	Type 1: CP (D, B)	Type1: CN (NB only if planned with original submission; NB w/NCA otherwise) (D, B)	Type 1: PCA (D, B)	Type 2: 180DS (D, B, IVP[a])
Shelf Life of the API Extend retest date	Type 2: MC (D, B)	Type 2: No submission; check/update internal procedures for API storage	Type 2	Type 2: CN (D, B) check/update internal procedures for API storage	Type 2: No submission; check/update internal procedures for API storage	Type 2: 30DN (D, B)
DCP formulation Change excipient ratio	Type 1: SC (D, B, IVP[a], C[a])	Type 1: CN (D, B, IVP[a], C[a])	Type 1: CP (D, B, IVP,C[a]) or new submission	Type 1: CN (NB w/NCA) (D, B, IVP[a], C[a])	Type 1: PCA (D, B, IVP[a], C[a])	Type 1: 180DS (D, B, IVP[a], C[a])
DCP formulation Change excipient(s)	Type 1: SC (D, B, IVP[a], C[a])	Type 1: CN (D, B, IVP[a], C[a])	Type 1: CP (D, B, IVP,C[a])	Type 1: CN (NB w/NCA) (D, B, IVP[a], C[a])	Type 1: PCA (D, B, IVP[a], C[a])	Type 1: PMA/180DS (D, B, IVP[a], C[a])
DCP formulation Change to a new API including within the same API family	Consultation with the TGA to determine if a new product application is needed (D, B, IVP[a],C[a])	Type 1: CN (D, B, IVP, C)	Type 1: CP (D, B, IVP,C[a]) or a new submission	Consultation with NB and NCA to determine if new product application is needed (D, B, IVP[a], C[a])	Type 1: PCA (D, B, IVP[a], C[a])	

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Supplier: Critical DCP components	Type 1: SC (D, B)	Type 2: No submission; Check/update internal procedures	Type 2	Type 1: CN (NB w/NCA) (D, B)	Type 1: PCA (D, B, IVP[a])	Type 1: 180DS (D, B)
Supplier: Non-critical DCP components	Type 2: MC (D)	Type 2: No submission; Check/update internal procedures	Type 2	Type 2: No submission (can be audited by NB at periodic audit)	Type 1: PCA (D, B[a], IVP[a])	Type 1: AR/30DN (D, B[a])
Manufacturing site: DCP	Type 1: SC (D, B)	Type 1: CN (with audit) (D)	Type 2	Type 1: Same process/ equipment: CN to NB (D, B) Type 1: Process/ equipment changes CN (w/NCA[a]) (D, B)	Type 1: PCA (D)	Type 1: Site change 180DS (D, B)
Manufacturing site: DP (change to interface with the DCP)	Type 1: SC (D, B)	Type 1: CN (w/audit[a]) (D)	Type 2	Type 1: Same process/ equipment: CN to NB (D,B)	Type 1: PCA (D)	Type 1: Site change 180DS (D, B)
Manufacturing site: VDDCP	Type 1: SC (D, B)	Type 1: CN (w/audit) (D)	Type 1: CP (D) (w/audit)	Type 1: Same process / equipment: CN to NB (D, B) Type 1: Process/ equipment changes CN (w/NCA[a])(D, B)	Type 1: PCA (D)	Type 1: Site change 180DS (D, B)

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Manufacturing: DCP methods	Type 1: SC (D, B, IVP[a], C[a])	Type 1: CN (D, B[a], IVP[a])	Type 2	Type 1: CN (NB w/NCA)	Type 1: PCA (D, B[a])	Type 1: AR/30DN/180DS (D, B, IVP[a], C[a])
Manufacturing: Process technology	Type 1: SC (D, B, IVP[a], C[a])	Type 1: CN (D, B, IVP[a])	Type 2	Type 1: CN (NB w/NCA) (D, B, IVP[a])	Type 1: PCA (D, B, IVP[a])	Type 1: AR/30DN/180DS (D, B, IVP[a], C[a])
Manufacturing: Sterilization process	Type 1: SC (D, B)	Type 1: CN (D, B)	Type 2	Type 1: CN (NB w/NCA) (D, B)	Type 1: PCA (D, B)	Type 1: AR/30DN/180DS (D, B, IVP[a], C[a])
Test method: Replace method	Type 1: SC (D, B)	Type 2: No submission; check/update internal procedures Type 1: CN If not pharmacopeial method (D, B, IVP[a])	Type 1: CP (D, B)	Type 1: CN (NB w/NCA[a]) (D, B)	Type 1: PCA (D, B, IVP[a])	Type 1: 30DN (D, B)
Test method: Frequency or sample size	Type 1: SC (D, B)	Type 2: No submission; check/update internal procedures	Type 1: CP (D, B)	Type 1: From per-Lot to periodic/stability CN (NB w/NCA[a]) (D, B)	Type 1: PCA (D, B, IVP[a])	Type 3: AR – increased frequency/sample size (D, B) Type 1: 30DN (D, B)

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Test method: Method procedures	Type 1: SC (D, B)	Type 2: No submission; check procedures at audit Type 1: If not pharmacopeial method: CN (D, B, IVP[a])	Type 1: CP (D,B)	Type 1: CN (NB w/NCA[a]) (D, B) If only DP-related: Type 2: CN (D, B)	Type 1: PCA (D, B)	Type 1: AR/30DN (D, B[a])
Packaging: System	Type 1: SC (D, B)	Type 1: CN (D, B)	Type 1: CP (D,B)	Type 1: CN (D, B)	Type 1: PCA (D, B[a])	Type 1: RT/180DS (D, B)
Packaging: Method/process	Type 1: SC (D, B)	Type 1: CN (D, B)	Type 2	Type 1: CN (D, B)	Type 1: PCA (D, B[a])	Type 1: AR/RT/180DS (D, B[a])
Packaging: Storage conditions	Type 1: SC (D, B)	Type 1: CN (D, B)	Type 1: CP [a](D,B)	Type 1: CN (NB w/NCA[a]) (D, B)	Type 1: PCA (D, B)	Type 1: RT/180DS (D, B)
Change indication: For use	Type 1: SC (D, B, IVP[a], C[a])	Type 1: CN (D, B[a], IVP[a], C[a])	Type 1: CP (D, B, IVP, C[a])	Type 1: CN (NB w/NCA[a]) (D, C, IVP[a])	Type 1: PCA (D, B[a], IVP[a], C[a])	Type 1: 180DS/180PT/ PMA (D, B[a], IVP[a], C[a])

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Change indication: IFU label	Type 1: SC (D, B, IVP[a], C[a])	Type 1: CN Contraindications, warnings/precautions (D, C[a]) Type 1: CN Minor changes to wording (D)	Type 1: CP (D, B, IVP, C[a])	Type 1: CN (NB w/NCA[a]) (D)	Type 1: PCA (D, B[a], IVP[a], C[a])	Type 3: SPEC for adding safety info (D, B[a], IVP[a], C[a]) Type 1: RT/180DS (D, B[a], IVP[a], C[a])

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Type 3: consult regulatory body

[a] Contact with the regulatory authority can be necessary for the final determination of whether that type of information is needed.

NOTE 1 The information in this table is intended for information purposes and is current at the time of the publication of this document but can become outdated and cannot be considered as prescriptive or exhaustive.

NOTE 2 Users of this table can consult the regulatory body for the country of submission in order to confirm current requirements.

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[3] ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes*

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[21] ISO 16429, *Implants for surgery — Measurements of open-circuit potential to assess corrosion behaviour of metallic implantable materials and medical devices over extended time periods*