

**Considerations on regulatory requirements for
registration of drug-device combination products in
Canada and the European Union**

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Table of Contents

List of Abbreviations	V
List of Figures	VIII
List of Tables.....	VIII
Acknowledgements	IX
1. Introduction	1
2. Canada.....	2
2.1. Responsible Regulatory Bodies	2
2.2. Health Canada	2
2.2.1. Health Canada’s Regulatory Role.....	2
2.2.2. Regulating Health Products	3
2.2.3. Health Products and Food Branch	4
2.2.3.1. Therapeutic Products Directorate	5
2.2.3.2. Biologics and Genetic Therapies Directorate.....	5
2.2.3.3. Directorate for Medical Devices.....	5
2.3. Drugs and Health Products Legislation and Guidelines	5
2.3.1. Food and Drugs Act.....	6
2.3.2. Food and Drug Regulations	6
2.3.3. Medical Devices Regulations.....	8
2.4. Combination Products.....	8
2.4.1. Legal Provisions	8
3. The European Union	18
3.1. Legislative Framework	18
3.2. Medicinal Products	19

3.3. Medical Devices	19
3.4. Drug–Device Combinations under MDD	20
3.5. The Consultation Process for Devices Incorporating a Medicinal Substance Having Ancillary Action under MDD.....	23
3.6. Drug–Device Combinations under MDR	26
3.6.1. Legal Stipulations	26
3.6.2. Integral DDCs	30
3.6.3. Non-Integral DDCs	31
3.6.4. Dossier Requirements for DDCs.....	32
4. Discussions.....	42
4.1. Canada	42
4.2. The European Union	43
5. Summary and Conclusions	47
Literature	X
Annexes.....	XVIII
Annex 1	XVIII
Annex 2	XXI
Annex 3	XXVI
Annex 4	XXIX

List of Abbreviations

21 CFR	Code of Federal Regulations – Title 21 - Food and Drugs
ADME	Absorption, Distribution, Metabolism and Elimination
AIMDD	Active Implantable Medical Devices
Art.	Article
ASMF	Active Substance Master File
AUC	Area Under the Curve
BGTD	Biologics and Genetic Therapies Directorate
BPWP	Blood Products Working Party
CA(s)	Competent Authority(ies)
CAGR	Compound Annual Growth Rate
CE	CE marking (Conformité Européenne (French))
CEP	Certificate of European Pharmacopeia (Certificate of Suitability)
CGTP	Cell and Gene Therapy Product
CHMP	Committee for Medicinal Products for Human Use
CPMP	Committee on Proprietary Medicinal Products
CQA	Critical Quality Attributes
Crt.	Criterion or Criteria
CTD	Common Technical Dossier
DDC	Drug-Device Combination
DDCP	Drug-Device Combination Product
Def.	Definition
DEL	Drug Establishment Licences
DIN	Drug Identification Number
DMD	Directorate for Medical Devices
DNA	Deoxyribonucleic Acid
e.g.	exempli gratia (Latin)
EC	European Commission
eCTD	Electronic Common Technical Dossier

EDQM	European Directorate for the Quality of Medicines and Healthcare
EEC	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EL	Establishment Licences
EMA	European Medicines Agency
EMEA	European Medicines Agency (<i>Institution changed its name in the meantime to EMA</i>)
EU	European Union
FDLI	Food and Drug Law Institute
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practices
GSPR	General Safety and Performance Requirements
HCP	Healthcare Professionals
HPFB	Health Canada's Health Products and Food Branch
ICH	International Council for Harmonisation
ICH Q10	Guideline on Pharmaceutical Quality System
IFU	Instructions for Use
Im	Medical device of (risk) class I with measuring function
INN	International Nonproprietary Names
Irsi	Reusable surgical instruments of (risk) class I
Is	Sterile medical device of (risk) class I
ISCT	International Society for Cell & Gene Therapy
IVDMD	Council Directive 98/79/EC on In Vitro Diagnostic Medical Devices
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MDD	Council Directive 93/42/EEC on Medical Devices
MDEL	Medical Device Establishment Licence
MDL	Medical Device Licence
MDR	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (short: Medical Device Regulation)

MDSAP	Medical Device Single Audit Programme
MEDDEV	European Medical Device Vigilance System
MPD	Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (short: Medicinal Products Directive)
MQEG	Manufacturing & Quality Expert Group
MRA	Mutual Recognition Agreements
NB	Notified Body
NBOP	Notified Body Opinion
NOC	Notice of Compliance
OSIP	Office of Submissions and Intellectual Property
Ph. Eur.	European Pharmacopoeia
PMA	Principal Mechanism of Action
PMF	Plasma Master File
PQS	Pharmaceutical Quality System
QMS	Quality Management System
RAPS	Regulatory Affairs Professionals Society
SDN	Screening Deficiency Notice
SmPC	Summary of Product Characteristics
SWP	Safety Working Party
TPCC	Therapeutic Products Classification Committee
TPD	Therapeutic Products Directorate
TSE	Transmissible Spongiform Encephalopathy
US-FDA	The United States of America - Food and Drug Administration
vCJD	Variant Creutzfeldt–Jakob disease

List of Figures

Figure 1 – Canada’s Minister of Health schematic	3
Figure 2 – The Canadian regulatory framework	6
Figure 3 – Classification flow of a drug-medical device combination	15
Figure 4 – A section of the Drug Submission Application Form for Human, Veterinary or Disinfectant Drugs and Clinical Trial Application/ Attestation	16
Figure 5 – Drug-device combinations as regulated by MDD	22
Figure 6 – Consultation procedure on medical devices incorporating, as an integral part, an ancillary medicinal substance according to MDD and MDR	25
Figure 7 – Drug-device combinations as regulated by MDR	30

List of Tables

Table 1 – Summary of changes for Marketing Authorisations Applications involving integral DDCs	29
Table 2 – Specific requirements for integral DDC to be enclosed in Module 1 of the eCTD dossier	32
Table 3 – Specific requirements for integral DDC to be enclosed in Module 3 of the eCTD dossier	33
Table 4 – Specific requirements for non-integral DDC to be enclosed in Module 1 of the eCTD dossier	38
Table 5 – Specific requirements for non-integral DDC to be enclosed in Module 3 of the eCTD dossier	39

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1. Introduction

The aim of the present work is to compile relevant, in particular regulatory aspects regarding combination products in Canada and the European Union, to understand and present which is the current situation and identify the challenges, to reveal the similarities and differences, and to note whether the manufacturers can export their approved products in one of the regions, to the other area.

The reason why the work theme of this master thesis was chosen is because the combination products are very much in demand nowadays as they are innovative products designed to increase the therapeutic effectiveness by combining the potential of an active pharmaceutical ingredient (drug or biological) and a medical device resulting in an enhanced effect of the new products.

Recent research suggests that up to 30% of pharmaceutical research and development is now directed toward combination products which may require new legislation to be appropriately handled as it is mentioned in “*Public Health Effectiveness of the FDA 510(k) Clearance Process*” *Workshop Report* (see chapter 5 – *The Global Framework for Regulation of Medical Devices, para Combination Products*). [1]

The global drug-device combination products market was valued at \$81,374 million in 2017 and is projected to reach \$139,193 million by 2025 at a Compound Annual Growth Rate (CAGR) of 6.9% from 2018 to 2025. [2]

Even though it was intended to cover with this study more world's regions it was shown during the preliminary research phase that the realm of the drug-device combination products' regulation is more complex than expected therefore, only one region beside EU has been explored. From few other world regions under the initial spotlight, Canada has been chosen as it has a long history in regulating and dealing with combination products in contrast with the emerging regulation of the European Union which is still optimizing its approach and regulatory framework on this domain.

2. Canada

2.1. Responsible Regulatory Bodies

In Canada, the responsibility of regulating, protecting and improving the quality of “health” products like medicinal products or medical devices is given to the Minister of Health supported by the Health Portfolio, which consist of five departments: the Canadian Food Inspection Agency, the Canadian Institutes of Health Research, Health Canada, the Patented Medicine Prices Review Board and the Public Health Agency of Canada. [3]

2.2. Health Canada

Health Canada is a department formed in June 1993 responsible for the national public health, to give peoples timely, safe and secure access to foods, drugs, medical devices, and cosmetics. It is organized in branches, offices, and bureaus to ensure compliance with federal law in a variety of healthcare, agricultural and pharmaceutical activities, as well as regulate facilities involved in health research and pharmaceutical drug manufacturing and testing. Figure 1 outlines a schematic composition of Health Canada. [4] [5]

2.2.1. Health Canada’s Regulatory Role

Health Canada oversees the federal government's jurisdictions in all areas of health care in Canada and governs nationwide standards of medical service established in the Canada Health Act. Among others, department’s specific responsibilities include communication and distribution of information to support disease prevention, regulation of food, drugs, and environmental safety. [4] [6]

Health Canada, in its regulatory role:

1. regulates product safety by setting and enforcing requirements for all products sold in Canada: foods, health products, consumer products etc.
2. investigates complaints about unsafe products and conducts inspections to confirm that companies are following rules for product safety.
3. develops guidelines for reducing the environmental risks in order to help keep water and air pollution low and protect population against dangerous substances.
4. provides population with information on food safety and on choosing and using consumer products safely. [7] [8]

2.2.2. Regulating Health Products

Health Canada ensures that the health products sold in Canada are safe, real and of high quality. This objective is achieved by creating policies and establishing standards, approving health products, monitoring safety and quality, promoting and enforcing compliance. According to Health Canada's website, a schematic of the Minister of Health is depicted in Figure 1.

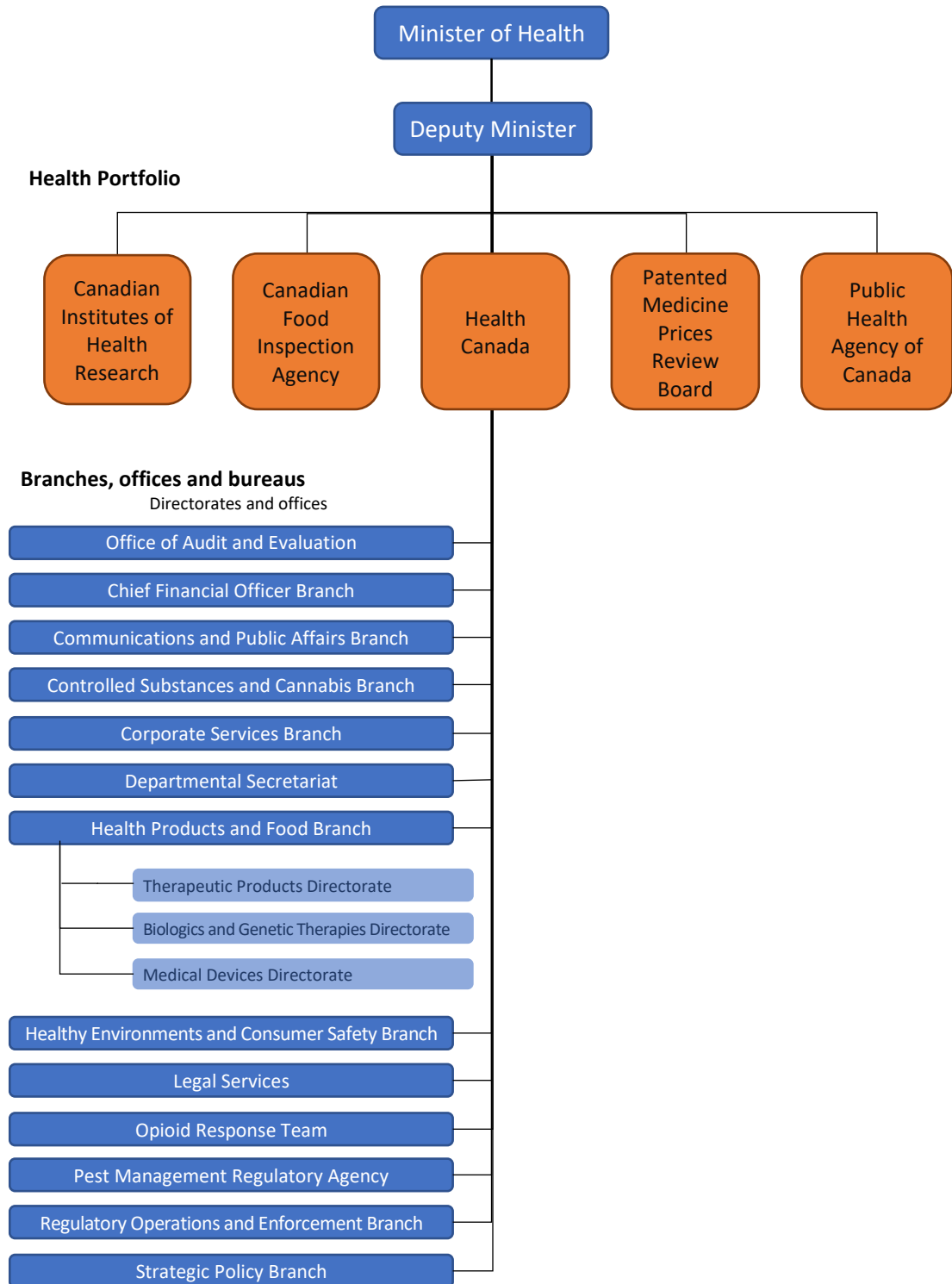


Figure 1 – Canada's Minister of Health schematic (presentation by the author)

1. Creating policies and setting standards

All health products must meet the requirements of the Food and Drugs Act and its regulations in order to be legally sold in Canada. To help companies understand their requirements and responsibilities more clearly, Health Canada produces policies, standards, guidance documents.

2. Approving health products

Health Canada regulates and approves for selling drugs (medicinal products), medical devices, and natural health products assessing if its benefits outweigh its risks, the evidence supports its health claims, and the risks and uncertainties can be managed. [9]

Drug products include over-the-counter drugs, which are medications available without a prescription, prescription drugs, which are medications available only by prescription, and biologics.

Medical devices include hospital beds, dental devices, household items, complex technologies, surgical implants and prosthetics, and diagnostic equipment and test kits.

Natural health products include homeopathic medicines, vitamins, minerals and herbal remedies, traditional medicines, and probiotic supplements and other products like amino acids and essential fatty acids. [10]

3. Monitoring safety and quality

Health Canada monitors the safety a product once it is authorized for sale, through safety reviews, companies' reports on the safety of their products, evaluations of changes to product formulas or designs, assessments of complaints and adverse reaction reports from companies, patients and consumers, and health professionals.

4. Promoting and enforcing compliance

Health Canada helps make sure companies and products meet Canada's high safety and quality standards by promoting and enforcing compliance with laws and regulations. Health Canada conducting inspections checks clinical trials, drug companies, medical devices, blood establishments, cells, tissues and organs, donor semen establishments.

2.2.3. Health Products and Food Branch

Health Canada's Health Products and Food Branch (HPFB) is the national regulatory authority accountable for evaluating and monitoring the quality, safety, and efficacy of health products, foods, and veterinary drugs (therapeutic products) in Canada. [11] HPFB's mandate is to manage the health-related risks and benefits of health products and food by minimizing

health risk factors to citizens while maximizing the safety provided by the regulatory system for health products and food.

HPFB activities are performed by more directorates including Biologics and Genetic Therapies Directorate, Therapeutic Products Directorate and Directorate for Medical Devices. [12]

2.2.3.1. Therapeutic Products Directorate

The Therapeutic Products Directorate (TPD) is Canada's regulator of prescription drugs and medical devices for human use by assessing the scientific evidence of the product's safety, effectiveness, and quality, as required by the Food and Drugs Act and Regulations. [13]

2.2.3.2. Biologics and Genetic Therapies Directorate

Health Canada's Biologics and Genetic Therapies Directorate (BGTD) is the Canadian regulatory authority of biological drugs and radiopharmaceuticals for human use. [14]

2.2.3.3. Directorate for Medical Devices

The Directorate for Medical Devices (DMD) was created on November 21st, 2019 within the HPFB with the purpose of regulating medical devices during their entire life cycle by bringing together specific post-market with pre-market activities. [15] [16]

2.3. Drugs and Health Products Legislation and Guidelines

Health Canada develops and enforces regulations under Government of Canada legislation by consultation with the Canadian public, industry and other interested parties in the development of acts and regulations that protect health and safety. Moreover, prepares guidelines and policies in order to help interpret and clarify the legislation surrounding drugs and health products. Schematically, the regulatory framework is represented in Figure 2. [17]

Acts are laws enacted by Parliament which create standards of general applicability with binding legal effect on all Canadians and are unlikely to change in the medium term. [17]

Regulations are rules enacted by the Parliament of Canada which have the force of law and contain more specific guidelines than Acts including definitions, licensing requirements, performance specifications, exemptions, forms and other details. [18]

Guidelines and Policies reflect departmental Policy and express recommended standards that derive from Legislation. They do not have the force of law or regulation, are of general applicability for either internal or public

purposes and explain how various laws will be interpreted by the relevant agency. [17] [19]

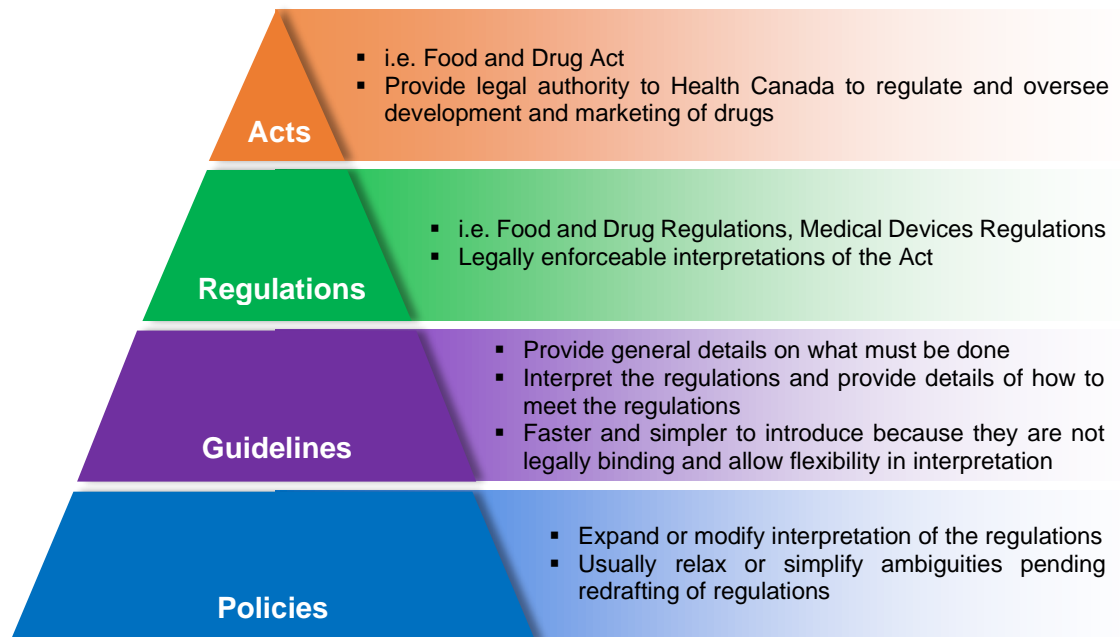


Figure 2 – The Canadian regulatory framework comprises of Acts, Regulations, Guidelines and Policies [61]

2.3.1. Food and Drugs Act

The Food and Drugs Act was adopted in 1920 by the Parliament of Canada and focus on the manufacture, trade, transportation and sale of food, drugs, medical devices and cosmetics. The legislation requires manufactures to file submissions before marketing their drug and entitles the Minister of Health to cancel or suspend a license for disobeying the requirements set out in regulations.

Regulation governing food, drugs, cosmetics and therapeutic devices is found in Part I of the Food and Drugs Act. Section 9 (1) of the Act prohibits misleading representation of these products. [20]

All federal Acts and regulations maintained by the Department of Justice are available on the Justice Laws website in the official consolidated version as 1st of June 2009 indicating that they can be used for evidentiary purposes. [21]

2.3.2. Food and Drug Regulations

The Food and Drug Regulations elaborate principles or rules designed to control or govern conduct with respect to food, drugs, medical devices and cosmetics. They set out requirements for the manufacture, packaging, labelling, storage, importation, distribution and sale of prescription and non-prescription drugs in Canada as well as conditions for drug clinical trials.

Part A of the Food and Drug Regulations consists of prohibitions, powers, definitions and obligations that generally apply throughout the regulations, Part B refers to food while Part C deals with drugs and includes the following Divisions:

Division 1 – General; It outlines the requirements for sale or importation of drugs, enclosing labelling, packaging, testing, advertising and post-authorization obligations including adverse drug reaction reporting. It also describes the requirements for obtaining, renewing, updating and cancelling a Drug Identification Number (DIN) which is required in order to sell a drug in Canada¹.

Division 1A – Establishment Licences (EL); A drug EL is required for any person fabricating, packaging, labelling, testing, importing or distributing drugs, or wholesaling certain drugs in Canada. This division sets out procedures related to its applications, renewals, suspensions and cancellations.

Division 2 – Good Manufacturing Practices (GMP); Division 2 sets out the GMP standards that apply to all activities in the drug supply chain: fabricating, testing, importing, packaging, labelling, storing, and transporting of the drug. to ensure that drugs are consistently produced and controlled to meet quality standards.

Division 3 – Schedule C Drugs; It sets out specific requirements for radiopharmaceutical drugs.

Division 4 – Schedule D Drugs; It sets out specific requirements for biologic drugs.

Division 5 – Drugs for Clinical Trials Involving Human Subjects; It provides a mechanism to regulate the sale or importation of drugs used for clinical trials in humans and helps protect patients participating in these trials.

Division 6 – Canadian Standard Drugs; It sets standards for six specified drugs (conjugated estrogens, digitoxin, digoxin, esterified estrogens, gelatin and thyroid), using specific well-established standards for these drugs.

Division 7 – Sale of Drugs for the Purposes of Implementing the General Council Decision; It provides the rules for a manufacturer to export, for humanitarian purposes, a drug that cannot be sold in Canada due to patent restrictions. This provision permits access to lower cost generic drugs in regions of the world, such as emerging nations, where the drug would otherwise be unavailable.

Division 8 – New Drugs; It includes drugs that have not been sold in sufficient quantity or for sufficient time to establish their safety and effectiveness. This

¹ A Drug Identification Number (DIN) is a computer-generated eight-digit number assigned by Health Canada to a drug product prior to being marketed in Canada. It uniquely identifies all drug products sold in a dosage form in Canada and is located on the label of prescription and over-the-counter drug products that have been evaluated and authorized for sale in Canada. [60]

division sets out the pre- and post-authorization requirements for new drugs and adds to the requirements found in Division 1. It also includes requirements for extraordinary use new drugs, clinical testing and experimental studies.

Division 9 – Non-prescription drugs; It sets out additional requirements for a few commonly used non-prescription pain or fever medications for human use. [22]

2.3.3. Medical Devices Regulations

These Regulations apply to the sale and advertising for sale of a medical device and the importation of a medical device for sale or for use on individuals, other than importation for personal use. [23] It is structured as follows:

PART 1 – General; It applies to medical devices that are not subject to Part 2 or 3.

PART 2 – Custom-Made Devices and Medical Devices to Be Imported or Sold for Special Access; It applies to custom-made devices and medical devices that are to be imported or sold for emergency use or if conventional therapies have failed, are unavailable or are unsuitable.

PART 3 – Medical Devices for Investigational Testing Involving Human Subjects; It applies to medical devices that are to be imported or sold for investigational testing involving human subjects.

PART 4 – Export Certificates; It sets out the form to be used for an export certificate for medical devices.

PART 5 – Transitional Provisions, Repeal and Coming into Force. [24]

2.4. Combination Products

2.4.1. Legal Provisions

The combination products in Canada are regulated by a Policy, consisting of the documents:

- a) Drug/Medical Device Combination Products Policy – sets the requirements that a combination of drugs and devices should meet as to be considered and registered like a “combination product”; [25]
- b) Policy on Drug/Medical Device Combination Products – Decisions – encloses the classification provided by the TPD in line with Drug/Medical Device Combination Products Policy with examples of combinations that fall under this Policy and situations where its statements are not applicable. [26]

Document a) was revised and become effective as of March 1, 2006 and replaced the previous one dated May 13, 1999. A change in regulation for drug-device combination products started in 1998 when some devices of this type were classified as drugs and some products put under medical device category as notified in a Policy on Drug/Medical Device Combination Products

issued in October 20, 1998. The Policy was revised from time to time and in March 2006 became a Policy of Health Canada.

The purpose of this Policy is to ensure timely access to drug-medical device combination products by establishing a single window approach and more efficient submission processing system, to guarantee that combination products marketed in Canada are safe, effective, and of high quality and to harmonize regulatory requirements with both the United States and European Union as to assist in the development of mutual recognition agreements with those jurisdictions.

Before 2006, a sponsor of drug-medical device combination products had to satisfy the requirements of two sets of regulations. The drug component of a combination product had to comply with the Food and Drug Regulations, and the device component with the Medical Device Regulations. Later, the TPD and the BGTD understanding the regulatory burden that this created for sponsors and the discouragement it presented to marketing combination products in Canada, assessed that the risks associated with a combination product could be managed appropriately under one set of regulations and the Drug/Medical Device Combination Products Policy was issued.

The Policy is not applied retrospectively to products already classified as drugs or devices however, the Directorates reserve the right to reclassify products where the continuing classification status results in unfair or unreasonable application of fees or other regulatory requirements. This Policy does not apply to combinations of drugs and medical devices where the drug component and the device component can be used separately (e.g. products sold together in procedure packages and trays). The Food and Drug Regulations shall apply to the drug component of such a combination and the Medical Devices Regulations shall apply to the device component. [25]

The Policy provided a clear definition for combination products:

“Is a therapeutic product that combines a drug component and a device component (which by themselves would be classified as a drug or a device), such that the distinctive nature of the drug component and device component is integrated in a singular product.” [25]

With the announcement of this Policy, drug/device combination product classification decision will be considered by the *principal mechanism of action (PMA)* from which the claimed effect or purpose of the product is achieved. The entire product will be then regulated under either the Food and Drug Regulations or the Medical Devices Regulations.

However, in order to be considered as a combination product, every component has to meet first the “Device” and “Drug” definitions under Food & Drug Act and its associated regulation. Section 2 of the Act defines a device and a drug as follows:

“Device means an instrument, apparatus, contrivance or other similar article, or an *in vitro* reagent, including a component, part or accessory of any of them, that is manufactured, sold or represented for use in

- (a) *diagnosing, treating, mitigating or preventing a disease, disorder or abnormal physical state, or any of their symptoms, in human beings or animals,*
- (b) *restoring, modifying or correcting the body structure of human beings or animals or the functioning of any part of the bodies of human beings or animals,*
- (c) *diagnosing pregnancy in human beings or animals,*
- (d) *caring for human beings or animals during pregnancy or at or after the birth of the offspring, including caring for the offspring, or*
- (e) *preventing conception in human beings or animals;*

however, it does not include such an instrument, apparatus, contrivance or article, or a component, part or accessory of any of them, that does any of the actions referred to in paragraphs (a) to (e) solely by pharmacological, immunological or metabolic means or solely by chemical means in or on the body of a human being or animal;” [27]

The Food and Drugs Act was amended in 2014 by the Protecting Canadians from Unsafe Drugs Act (Vanessa’s Law). [28] One of the changes refers to the definition of “device” which has been slightly modified. The last paragraph of the definition supports differentiating between “device” and “drug” by listing drug indicia. [27]

“Drug includes any substance or mixture of substances manufactured, sold or represented for use in

- (a) *the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,*
- (b) *restoring, correcting or modifying organic functions in human beings or animals, or*
- (c) *disinfection in premises in which food is manufactured, prepared or kept;” [27]*

Even if the definition not explicitly mention “substances” or “materials” or similar, substances might also be medical devices as to the Health Canada Guidance Document “Classification of Products at the (Medical) Device-Drug Interface” [27], where its chapter 2.4 lays down:

“The current definition of “device” in the Food and Drug Act explicitly excludes products that accomplish their effect “solely by pharmacological, immunological or metabolic means or solely by chemical means in or on the body of a human being or animal. This

wording allows for some substances to be classified as medical devices. Specifically, a substance could be a device if its mode of action were not accomplished by pharmacological, immunological or metabolic means, or by chemical means in or on the body. However, this should not be interpreted as suggesting that every substance that does not act by pharmacological, immunological, metabolic, or by chemical means in or on the body, is a medical device. Instead, the entirety of the respective definition of “device” and “drug” must be considered when determining whether a substance is a device or a drug”. [27]

An example where a substance-based product is classified as medical device is presented on the next page (a liquid for use as a body cavity filler).

Definitions of device and drug consider how a product achieves its therapeutic function, plus how its composition and characteristics are both represented and perceived in the marketplace.

The key for the distinction between medicinal product (drug) and medical device, therefore, lies in the interpretation of the main concepts that define them: therapeutic effect and mechanism of action. Medical devices and medicinal products share the common essence of having a therapeutic effect, while they are different for the mechanism of action with which they reach their effect.

In most cases, the distinction between devices and drugs is clear and these products can be easily classified according to the definitions. As new health products and technologies emerge, however, it is sometimes difficult to identify the appropriate regulatory framework that applies. In circumstances where a product does not clearly fall under the existing definitions, Guidance Document: Classification of Products at the (Medical) Device-Drug Interface is warranted on how classification decisions are likely to be made by Health Canada. [27]

This guidance is intended to assist in the classification of products at the device-drug interface when the appropriate regulatory framework is not immediately evident. However, the classification of device/drug combination products, which combine at least one device component and one drug component, is outside the scope of this guidance. A correspondent footnote gives a Note that, by Policy, unlike devices and drugs as single entities, a device/drug combination product is regulated under the regulatory framework that applies to its component that provides the greatest contribution to the desired effect with respect to an indication. [27]

Concerning drug-device combination products it is rather that above mentioned policies are relevant:

1. “Where the principal mechanism of action by which the claimed effect or purpose is achieved by pharmacological, immunological, or metabolic means, the combination product will be subject to the Food and Drug

Regulations, unless that action occurs in vitro, without reintroducing a modified cellular substance to the patient, in which case the product will be subject to the Medical Devices Regulations.”

2. *”Where the principal mechanism of action by which the claimed effect or purpose is **not** achieved by pharmacological, immunological, or metabolic means, but may be assisted in that effect or purpose by pharmacological, immunological, or metabolic means, the combination product will be subject to the Medical Devices Regulations.” [25]*

Immunological. Is understood as an action in or on the body by stimulation and/or mobilisation of cells and/or products involved in a specific immune reaction.

Metabolic. Is understood as an action which involves an alteration of the normal chemical processes participating in, and available for, normal body function. The fact that a product is itself metabolized does not imply that it achieves its principal intended action by metabolic means.

Pharmacological. Is understood as an interaction between the molecules of the substance in question and a cellular constituent, usually referred to as a receptor, which either results in a direct response, or which blocks the response to another agent and, for the purposes of this Policy, includes anti-infective activity. [25]

The Drug/Medical Device Combination Products Policy does not include any reference to the “chemical means” because its last revised version has been released in July 2014 while the Food and Drugs Act was amended later in 2014 by Vanessa’s Law which changed the definition of “device” and listed new indicia on “drug”.

However, some suggestions regarding the regulation of drug-device combinations were reiterated by Guidance Document: Classification of Products at the (Medical) Device-Drug Interface, revised in 2018, intending to reflect the latest changes to Food and Drugs Act. This guidance mentions that the entire definitions of both device and drug are considered when determining which is the most applicable to a product and how it works. For example, a liquid for use as a body cavity filler, with no pharmacological, immunological, metabolic or chemical properties, could be classified as a drug when considering only paragraph (a) of the drug definition. However, since it is intended to play a structural role once it has filled the volume of a cavity, it is best characterized as an article that modifies a body structure which is consistent with paragraph (b) of the device definition. Therefore, such a product would more reasonably be classified as a device. [27]

The mechanism of action of a substance is defined in dictionaries and textbooks as the mechanism by which an active substance produces an effect on a living organism or in a biochemical system. The mechanism of action is usually considered to include an identification of the specific molecular targets to which

a pharmacologically active substance binds or whose biochemical action it influences; a general recognition of the broad biochemical pathways (such as DNA synthesis, protein synthesis, metabolic pathways), which are affected (inhibited or promoted) by a substance is termed its "mode of action". [29]

Cell and gene therapy products (CGTPs) and medical devices whose components are integrated into singular product are regulated as combination products. Where the principal mechanism of action for the claimed effect or purpose is achieved by pharmacological, immunological or metabolic means, the Food and Drugs Regulations apply; in certain other circumstances, the Medical Device Regulation may apply. [30]

The classification of a combination product – as drug or as medical device – is the most important step in its regulatory and development framework and should be addressed early on, either to support sale of the product or to support investigational testing of the product in Canada. The first step in determining classification of a combination products is to consult the Policy on Drug/Medical Device Combination Products – Decisions.

The following types of combination products were classified by the Therapeutic Products Classification Committee (TPCC) in accordance with the Drug/Medical Device Combination Products Policy. This list includes products which are not combination products but where the classification of either drug or device was difficult to determine.

A. Combination products that have been classified as drugs:

- prefilled syringes
- patches for transdermal drug delivery
- implants whose primary purpose is to release a drug
- wound dressings whose primary purpose is to deliver a drug
- dental products impregnated with a drug whose primary purpose is to deliver a drug
- red blood cell processing solutions
- contrast media
- peritoneal dialysis solutions
- alcohol swabs

B. Combination products that have been classified as devices:

- drug coated devices such as catheters, shunt sensors, or pacemaker leads
- drug impregnated devices
- wound dressings and surgical barriers containing an antimicrobial agent
- wound dressings whose primary purpose is to act as a barrier to pathogens
- blood bags containing anticoagulant or preservation solutions
- bone cement containing antibiotic - novel bone void fillers, e.g. collagen matrix with bone morphogenic protein

- injectable collagen
- sodium hyaluronate nasal solution
- urea breath test (accessory to device)
- device for ex vivo photodynamic cell processing

C. Combinations of drugs and devices to which this Policy does not apply, and which must comply with both the Food and Drug Regulations and the Medical Devices Regulations:

- kits (e.g. epidural tray containing drugs and devices; first aid kit containing a drugs and devices)

D. Products for which neither set of regulations apply:

- minimally manipulated tissue [26]

If the products are not listed here, obtaining the classification becomes an essential step. The flow chart presented on next page in Figure 3 illustrates the classification pathway in Canada for a DDC product.

For a combination product that has not been previously classified, sponsors or manufacturers may submit a written request for a classification decision to the relevant review Centre/ Bureau / Office or make a presentation to the TPD, BGTD or MDD, as appropriate, for the purpose of classifying the product in advance of filing a submission / application. Alternatively, sponsors may file a submission/application to the review Centre / Bureau / Office based on their own classification. [14] [31]

In those cases, the sponsor or manufacturer should provide the following information:

- name of the product and identification of the device/drug components,
- a synopsis of relevant data describing the mechanism of action of each component and the principal mechanism of action of the product, further on composition, study design, measurements of efficacy in terms of structural, pharmacologic, metabolic, immunologic and ADME (Absorption, Distribution, Metabolism and Elimination) studies conducted, toxicity studies, etc.

Submissions / applications for combination products will be handled in accordance with the Drug/Medical Device Combination Products Policy, by using the three criteria identified in the Policy Statement and subject to either the Medical Devices Regulations or the Food and Drug Regulations based on the principal mechanism of action by which the claimed effect or purpose is achieved. Both principal and ancillary components must meet acceptable standards of safety, efficacy and quality. Additional information to support the safety, efficacy, or quality of either component of the combination product may be requested during the review period.

If the submission / application was filed incorrectly, the sponsor or manufacturer will be notified.

If a submission requiring a classification decision has not been supported by a classification request and synopsis, the receiving Bureau will issue Screening Deficiency Notice (SDN).

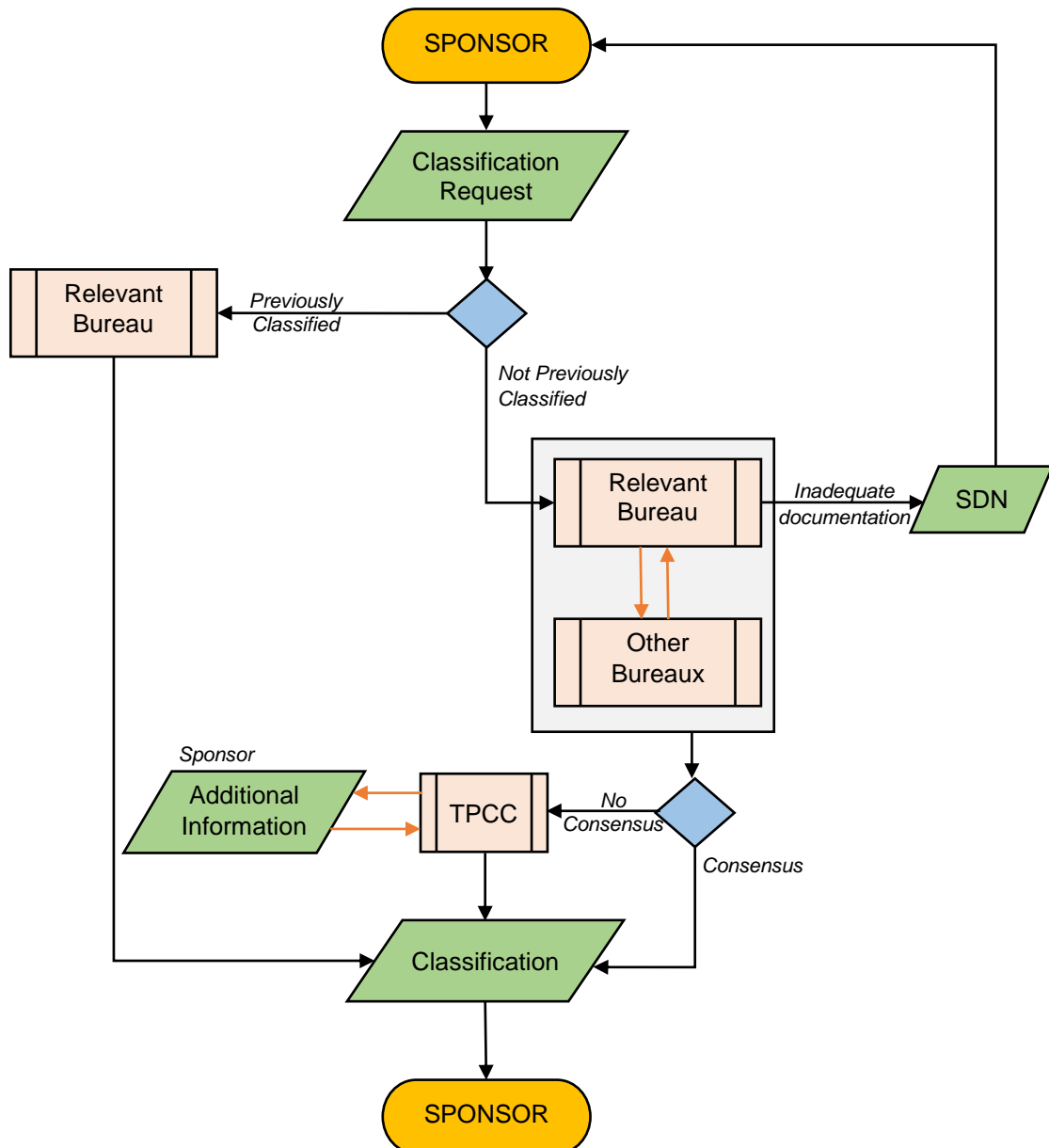


Figure 3 – Classification flow of a drug-medical device combination (presentation by the author) [25]

The receiving Bureau shall consult with other Bureaux affected and, in case of no consensus is reached on the classification of the combination product, the submission / application will be referred to the Therapeutic Products Classification Committee (TPCC) for a final decision. The TPCC then makes a recommendation to the Review Centre / Bureau / Office. The review of

submission for combination products will be undertaken according to the expertise required to assess the risk / benefit profile product.

TPCC is a committee appointed by the Director General of Therapeutic Products Directorate (TPD) and consists of representatives from various directorates within Health Products and Food Branch (HPFB). Its task is to develop, maintain, evaluate and recommend for approval policies, procedures and guidelines concerning the classification and review of therapeutic products as drugs, devices or combination products; to assess submissions for combination products referred to it and determine an appropriate classification and review mechanism for the submission. [32]

When a combination product is in compliance with the relevant Regulations, a Notice of Compliance will be signed by the Director General. A Notice of Compliance is a notification indicating that a manufacturer has complied to the *Food and Drug Regulations*. [33]

Submissions for combination products classified as drugs and regulated under the Food and Drug Regulations will be subject to any fees payable for drugs under the regulations enacted for that purpose. For a combination product classified as a drug, a submission or an application should be sent to the Office of Submissions and Intellectual Property (OSIP). The submission or application will be managed in accordance with Management of Drug Submissions and Applications guidance. [34]

A “Guidance for Completing the Drug Submission Application Form” available on the Health Canada web site indicates at Section # 64 how to fill in Application form (Figure 4) if the products is a drug and medical device combination, as follows “If the product is a drug and medical device combination, also indicate what type of drug it is, e.g. biologic/radiopharmaceutical or pharmaceutical”. [35]

61. Container Type	Package Size
62. Therapeutic/Pharmacological Classification	
63. Route(s) of Administration	
64. Drug Product <input type="checkbox"/> Biologic / <input type="checkbox"/> Radiopharmaceutical <input type="checkbox"/> Pharmaceutical <input type="checkbox"/> Disinfectant <input type="checkbox"/> Drug and Medical Device	
65. Drug Use <input type="checkbox"/> Human [<input type="checkbox"/> Paediatric (0-18 years of age) <input type="checkbox"/> Adult] <input type="checkbox"/> <input type="checkbox"/> Radiopharmaceutical <input type="checkbox"/> Veterinary <input type="checkbox"/> Disinfectant [<input type="checkbox"/> Hospital <input type="checkbox"/> Food Processing <input type="checkbox"/> Medical Instruments <input type="checkbox"/> Domestic <input type="checkbox"/> Barn <input type="checkbox"/> Institutional/Industrial <input type="checkbox"/> Contact Lens]	
66. Is this a Non-prescription drug to which one or more Schedule A claims apply? <input type="checkbox"/> Yes <input type="checkbox"/> No	

Figure 4 – A section of the Drug Submission Application Form for Human, Veterinary or Disinfectant Drugs and Clinical Trial Application/Attestation [63]

The Health Products and Food Branch of Health Canada, more precisely, under the Therapeutic Product Directorate or the Biologic and Genetic Therapies Directorate will review the products to ensure that they meet the requirements of the Food and Drugs Act. The information requested as part of the application must be detailed enough that Health Canada can make an assessment on the safety and effectiveness of the product. All submissions must be provided in an eCTD format. [36]

Following the review, if the HPFB concludes that drug's benefits outweigh its risks and that the risks can be mitigated, it officially approves the drug for sale in Canada by issuing a Notice of Compliance (NOC) and a Drug Identification Number (DIN). [37]

Combination products classified as drugs will be subject to Drug Establishment Licences (DEL) requirements of Part C Division 1A of the Food and Drug Regulations. Depending on the products, the medical device component can become a packaging material (e.g. when the medical device such as a syringe becomes the drug's immediate container). [38]

Submissions for combination products classified as devices and regulated under the Medical Devices Regulations will be subject to any fees payable for devices under regulations enacted for that purpose. For a combination product classified as a medical device, manufacturers are to submit a device license application to the Medical Devices Directorate as per the Guidance Document: Management of Applications for Medical Device Licenses. [39]

The Directorate ensures, to the extent possible, the safety, effectiveness and quality of medical devices in Canada by a combination of pre-market review, post-approval surveillance and quality systems in the manufacturing process. If the information provided meets the requirements of the Medical Devices Regulations, a Licence is issued. [40]

There are two types of licenses issued by Health Canada: the (1) *Medical Device Establishment Licence* (MDEL) required for Class I medical devices and the (2) *Medical Device Licence* (MDL) for all the other classes. [41]

From 1st January 2019 onwards any manufacturer selling medical devices into Canada must be part of the MDSAP programme. MDSAP is the Medical Device Single Audit Programme which consists of a single Quality Management System (QMS) audit for the following five regions: Australia, Brazil, Canada, Japan and the USA. The programme is voluntary for the other four regions, but Canada has mandated that manufacturers who sell medical devices (Class 2 or higher) in Canada after 1st January 2019 must have a QMS that has been approved through the MDSAP programme. [42] The MDSAP Audit model covers the requirements for combination products that are regulated as medical devices, and not those combination products, that are regulated as medicinal products.

TPD will maintain a list of products that the TPCC considers subject to the Food and Drug Regulations or the Medical Devices Regulations for the guidance of sponsors and Directorate staff.

A classification decision made for the purposes of investigational testing may change during the review phase of a submission on the basis of new information contained in the submission. [31] [25]

3. The European Union

3.1. Legislative Framework

Currently, the European Union specific regulatory framework does not include any official definition for the therapeutic products which result from a combination of a drug and a device. However, they are registered and regulated as medicinal products or medical devices based on their principal mode of action. Moreover, there are no specific regulations or regulatory body with precise jurisdiction for combination products. Nonetheless, the regulatory framework is set by directives, separately for drugs and medical devices and some cross-references and handled by appropriate authorities, as follows:

1. Medicinal products handled by national Competent Authorities (CA) and European Medicines Agency (EMA):
 - a. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, amended by Directives 2004/24/EC and 2004/27/EC;
 - b. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
2. Medical devices handled by Notified Bodies (NB):
 - a. Council Directive 90/385/EEC on Active Implantable Medical Devices (AIMDD);
 - b. Council Directive 93/42/EEC on Medical Devices (MDD);
 - c. Council Directive 98/79/EC on in vitro Diagnostic Medical Devices (IVDMD) amended by Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007;
 - d. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (MDR).

A "directive" is a legislative act that sets out a goal with more or less precise provisions that all EU countries must achieve but it is up to the individual countries to develop their own laws on how to reach these goals including the given provisions, while a "regulation" is a binding legislative act which must be applied in its entirety across the EU. [43]

3.2. Medicinal Products

The definition of medicinal product was issued originally in Directive 65/65/EEC and continued to the definition given in Directive 2001/83/EC (Medicinal Product Directive – MPD) lately amended by Directive 2004/27/EC. At Art. 1, a medicinal product is defined as:

*“(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.” [44]*

The current definition specifies the type of action a substance must exert to be considered a medicinal product, “by exerting a pharmacological, immunological or metabolic action”. A medicinal substance is thus a substance characterized as such not only based on its therapeutic purpose but also in view of its capacity to modify physiological functions through a specific mechanism of action, which may be pharmacological, immunological, or metabolic. [29]

3.3. Medical Devices

The definition of medical device, first reported in Directive 93/42/EEC (MDD), has undergone fewer modifications than the definition of medicinal product, the last one being published by MDR which supersedes all existing ones when enforced by May 2020.

At para 2 (a) Directive 93/42/EEC states that:

“Medical device means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- *diagnosis, prevention, monitoring, treatment, or alleviation of disease,*
- *diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,*
- *investigation, replacement or modification of the anatomy or of a physiological process,*
- *control of conception,*

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological, or metabolic means, but which may be assisted in its function by such means.” [45]

The current MDD definition has already delimited the purpose of medical devices on the basis of the mechanism of action, stating that a device: “does not achieve its principal intended action in or on the human body by pharmacological, immunological, or metabolic means, but which may be assisted in its function by such means”. [29]

3.4. Drug–Device Combinations under MDD

As noted, specific drug-device combination regulations do not currently exist in the EU however, the MDD establishes in some ways the regulatory pathway for combinations of products that have a medical device as a component. Thus, the definitions provided by paragraphs 3 and 4 of Art. 1 of the MDD indicate how different combinations should be considered:

“Where a device is intended to administer a medicinal product within the meaning of Article 1 of Directive 2001/83/EC, that device shall be governed by this Directive, without prejudice to the provisions of Directive 2001/83/EC with regard to the medicinal product.

If, however, such a device is placed on the market in such a way that the device and the medicinal product form a single integral product which is intended exclusively for use in the given combination and which is not reusable, that single product shall be governed by Directive 2001/83/EC. The relevant essential requirements of Annex I to this Directive shall apply as far as safety and performance-related device features are concerned.” [45]

According to the first part of the above quoted paragraph, a first category of drug-device combination could be identified. This situation is met when a device is intended to dispense a medicinal substance, but the respective medicinal substance is not an integral part of the device. In this case the device has to be treated as a medical device and governed by the MDD, while the medicinal substance is separately regulated by the Directive 2001/83/EC.

The second part of paragraph 3 introduces a second category of drug-device combination when the device and the medicinal substance together meet simultaneously the following criteria: form a single integral product, it is intended exclusively for use in the given combination and it is not reusable. In this situation, that single product is treated as a medicinal product and governed by Directive 2001/83/EC while the relevant essential requirements of Annex I of the MDD has to be applied with regard to the safety and performance of related device features.

“Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product within the meaning of Article 1 of Directive 2001/83/EC and which is liable to act upon the body with action ancillary to that of the device, that device shall be assessed and authorized in accordance with this Directive.”

Lastly, the paragraph 4 suggests a third category of drug-device combination that consists of a device which incorporates integrally a medicinal substance whose action is supplementary to that of the device. The medicinal substance incorporated in the device must meet the three following conditions: if used separately, may be considered to be a medicinal product, it is liable to act upon the human body, and its action is ancillary to that of the device. In this case the device has to be treated as a medical device and governed by the MDD. The quality, safety and usefulness of the medicinal substance must be verified by analogy with the methods specified in Annex I to Directive 2001/83/EC (para 7.4 of Annex I to MDD).

The above mentioned articles could be basically explained as meaning that, if a manufacturer intends to deliver a therapeutic with a device, but the therapeutic is not loaded, this combination is legislated as device (e.g. syringe) which is different from the situation when the therapeutic comes preloaded resulting in classifying the combination as medicinal product. However, if the manufacturer intends the delivery of the therapeutic as an ancillary action to that of the device, then the product is legislated as a medical device (e.g. drug delivery stent) (see chapter 18 – Regulation of drug-device combination products in Europe, subchapter 18.3 – Brief history of medicinal products and medical device legislation). [46]

MEDDEV 2.1/3 rev 3 guideline offers a list of examples of different drug-device combinations and how they are to be regulated:

a. Drug-delivery products regulated as medicinal products:

- *Prefilled syringes,*
- *Aerosols containing a medicinal product,*
- *Nebulizers pre-charged with a specific medicinal product,*
- *Patches for transdermal drug delivery,*
- *Implants containing medicinal products in a polymer matrix whose primary purpose is to release the medicinal product, e.g. plastic beads containing antibiotic for treating bone infections, or a matrix to release osteoinductive proteins into the surrounding bone,*
- *Intrauterine contraceptives whose primary purpose is to release progestogens,*
- *Single-use disposable iontophoresis devices incorporating a medicinal product,*
- *Wound treatment products comprising a matrix whose primary purpose is the administration of medicinal products, e.g. wound dressings containing an antimicrobial agent where the primary action of the dressing is to administer the agent to the wound as to control infection,*
- *Temporary root canal fillers incorporating medicinal products, whose primary purpose is to deliver the medicinal product.*

b. Drug-delivery products regulated as medical devices:

- *Drug delivery pump,*

- *Implantable infusion pump,*
 - *Iontophoresis device,*
 - *Nebulizer,*
 - *Syringe, jet injector,*
 - *Spacer devices for use with metered dose inhalers,*
 - *Port systems.*
- c. *Medical devices incorporating, as an integral part, an ancillary medicinal substance:*
- *Catheters coated with heparin or an antibiotic agent,*
 - *Bone cements containing antibiotic,*
 - *Root canal fillers which incorporate medicinal substances with ancillary action,*
 - *Soft tissue fillers incorporating local anaesthetics,*
 - *Electrodes with steroid-coated tip,*
 - *Wound dressings, surgical or barrier drapes (including tulle dressings) with antimicrobial agent,*
 - *Intrauterine contraceptives containing copper or silver,*
 - *Ophthalmic irrigation solutions principally intended for irrigation which contain components which support the metabolism of the endothelial cells of the cornea,*
 - *Drug eluting coronary stents.*

MEDDEV 2. 1/3 rev 3 is a guideline elaborated by a group of experts and is part of a set of Guidelines relating to questions of application of EC Directives on medical devices. Its aim is to provide useful direction to assist common positions to be taken throughout the EU and is expected to be followed within the Member States and, therefore, ensure uniform application of relevant Directive provisions. [47]

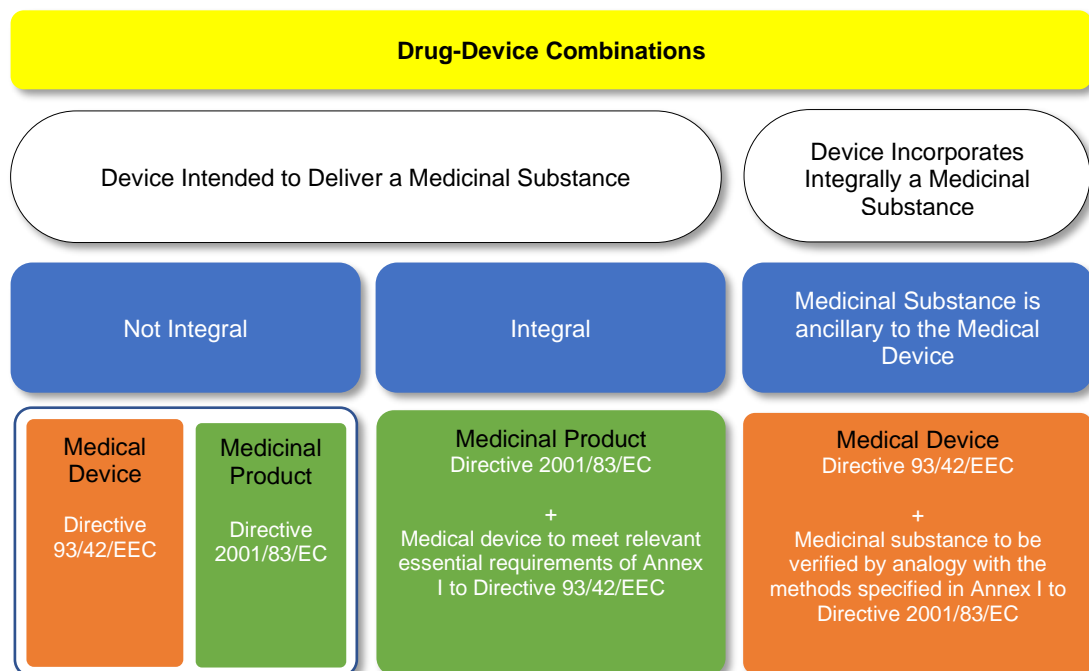


Figure 5 – Drug-device combinations as regulated by MDD [45] [48] [62]

3.5. The Consultation Process for Devices Incorporating a Medicinal Substance Having Ancillary Action under MDD

In a combination product, where medical devices are assisted in their function by pharmacological, immunological or metabolic means which are ancillary with respect to the principal intended action of the product, the product remains a medical device, and when it is principal then the product falls under the definition of a drug.

MEDDEV 2.1/3 rev. 3 outlines that the medical devices containing an ancillary medicinal substance should fulfil the MDD requirements but a CA to be consulted in reviewing the ancillary medicinal substance. This is known as the consultation procedure. The consultation procedure is only applicable for devices incorporating a substance which is liable to act upon the body with action ancillary to that of the device. [47]

The MDD introduces the subject of ancillary medicinal substances in section 7.4 of the essential requirements (Annex I), which states in part:

“Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product as defined in Article 1 of Directive 2001/83/EC and which is liable to act upon the body with action ancillary to that of the device, the quality, safety and usefulness of the substance must be verified by analogy with the methods specified in Annex I to Directive 2001/83/ EC.” [45]

“For devices incorporating, as an integral part, an ancillary medicinal substance, the notified body shall, having verified the usefulness of the substance as part of the medical device and taking account of the intended purpose of the device, seek a scientific opinion from one of the competent authorities or the EMEA [...] on the quality and safety of the substance including the clinical benefit/risk profile of the incorporation of the substance into the device. When issuing its opinion, the competent authority or the EMEA shall take into account the manufacturing process and the data related to the usefulness of incorporation of the substance into the device as determined by the notified body.” [47]

The consultation procedure is intended to determine whether the medicinal substance is suitable for its intended use in the medical device, and whether the risks of using the medicinal substance are justified by its benefits. It is important to note that the consultation procedure is between the NB and the CA, and not between the manufacturer and the CA. CAs may request whatever documentation they believe necessary to judge the drug's utility and safety for its intended purpose in the medical device.

The MEDDEV 2.1/3 rev. 3 guidance lists the data required in this dossier for the ancillary medicinal substance or the ancillary human blood derivative as incorporated in the medical device. These data are outlined in Annex 1, also attached to this thesis. [47]

Also, EMA provides with information on procedural aspects of the consultation procedure by notified bodies as well as data requirements for such application, in the guideline *“European Medicines Agency recommendation on the procedural aspects and dossier requirements for the consultation to the European Medicines Agency by a notified body on an ancillary medicinal substance or an ancillary human blood derivative incorporated in a medical device or active implantable medical device”*. Data requirements and format of the application dossier are drawn in Annex 2, also attached to this thesis. [48]

An overview of the consultation process on medical devices incorporating, as an integral part, an ancillary medicinal substance is presented in Figure 6 (see *chapter 18 – Regulation of drug-device combination products in Europe, subchapter 18.9 – Roles of notified bodies (NBs) vs. competent authorities (CAs)*). [46] [49]

The annex IX of MDD under Special Rules category, rule 13 of MDD classifies *“all devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in Article 1 of Directive 2001/83/EC, and which is liable to act on the human body with action ancillary to that of the devices as Class III”*. [45]

This is the highest medical device risk classification and, usually, to obtain the CE marking approval for Class III medical devices, the manufacturer must compile a design dossier to show evidence of conformity with the Essential Requirements described in Annex I of the MDD. The design dossier must be reviewed by a NB and a quality audit of the medical device manufacturer must be conducted by the NB.

The presence of the drug component brings more complexity to the CE marking approval process. The NB must consult a CA before taking a decision on providing CE mark certification. The manufacturer must compile a comprehensive dossier clearly describing the quality, safety and usefulness of the drug substance itself, and also on the drug as incorporated into the finished device. Additionally, the dossier for the drug product is created in accordance with the common technical dossier (CTD) format which is not typical for medical device manufacturers. [50]

According to the author, the MDR requirements for a consultation procedure are almost identical to those of the MDD.

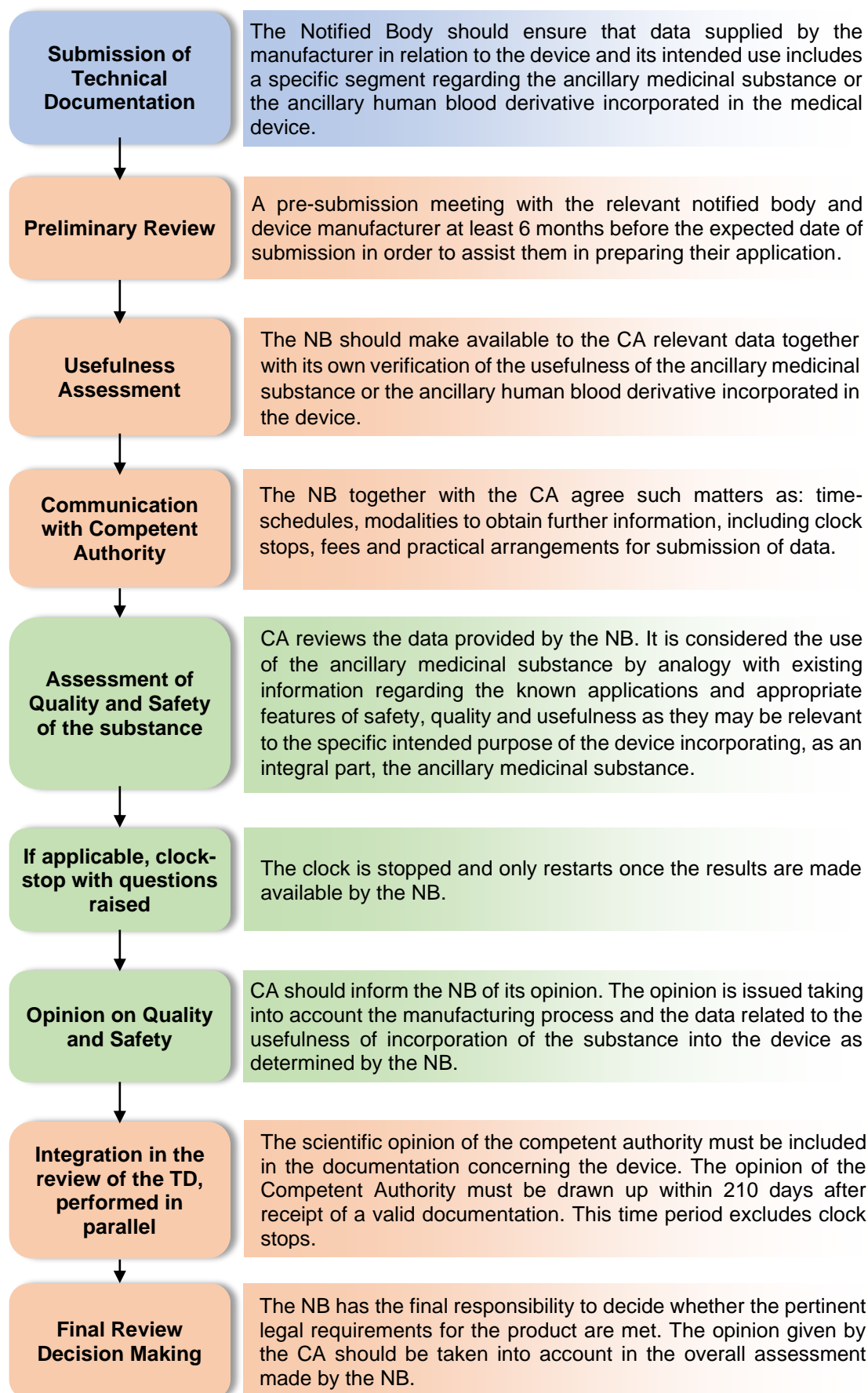


Figure 6 – Consultation procedure on medical devices incorporating, as an integral part, an ancillary medicinal substance according to MDD and MDR, based on [46] [47] [48] [49]

3.6. Drug–Device Combinations under MDR

3.6.1. Legal Stipulations

The adoption of Regulation (EU) 2017/745 on Medical Devices (*Medical Device Regulation – MDR*) extends the European legal framework for medical devices and, consequently for the medical devices combined with medicinal products or substances.

According to the MDR, the combined products continue to be regulated and registered either as medicinal products or medical devices, similar to the MDD, as it is stated in recital (10) of the MDR part with the justifications for the regulation (Whereas):

“Products which combine a medicinal product or substance and a medical device are regulated either under this Regulation or under Directive 2001/83/EC of the European Parliament and of the Council. ...”,

depending on which part (drug or device) contributes to the main effect to the therapeutic efficacy, and based on a consultative process and exchange of specific information for the two components, to ensure the compliance in terms of safety for such combination products.

In cases the combined products are subject to regulation as medicinal products (under Directive 2001/83/EC or Regulations (EC) No 726 / 2004), the medical device component should be compliant with the General Safety and Performance Requirements (GSPR) set by the MDR, but it should be assessed in the context of the MAA for such medicinal products. [51]

Similarly, to MDD, the MDR does not offer a precise definition for drug-device combination however, introduces new information regarding classification as medical device or medicinal product and sets the regulatory requirements for their components and the pathway to be followed for registration, under articles 1 (8) and 1 (9).

According to the way in which the medical devices along with medicinal products are placed on the market or put into service, two categories of combination products can be distinguished:

- I. where devices incorporate medicinal products as an integral part,
- II. where devices are intended to administer medicinal products.

I. Art. 1 (8) MDR presents the regulatory framework for the combination products with devices incorporating medicinal substances as an integral part:

“Any device which, when placed on the market or put into service, incorporates, as an integral part, a substance which, if used separately, would be considered to be a medicinal product as defined in point 2 of

Article 1 of Directive 2001/83/EC, including a medicinal product derived from human blood or human plasma as defined in point 10 of Article 1 of that Directive, and that has an action ancillary to that of the device, shall be assessed and authorised in accordance with this Regulation.” [51]

When the medicinal substance is ancillary, the combination product is regulated as a medical device and must be CE marked. However, the NB shall seek a scientific opinion from either the national CA or EMA before issuing a certificate for the combined product (so called consultation procedure, see Figure 6). The opinion from EMA is required for combined products, whose medicinal product part is falling exclusively within the scope of centralized procedure or incorporating human blood or plasma derivatives. In this case, NB should initiate the Consultation procedure for ancillary medicinal substances in medical devices and acts as the applicant on behalf of device manufacturer and follows EMA recommendation on the procedural aspects and dossier requirements. [47] [48] [52] [53]

The second part of Art. 1 (8) presents, in comparison to MDD, a new possibility to consider and regulate a combination as medicinal product namely, when the substance incorporated, as an integral part, in device has principal action.

“However, if the action of that substance is principal and not ancillary to that of the device, the integral product shall be governed by Directive 2001/83/EC or Regulation (EC) No 726/2004 of the European Parliament and of the Council (1), as applicable. In that case, the relevant general safety and performance requirements set out in Annex I to this Regulation shall apply as far as the safety and performance of the device part are concerned.” [51]

II. The regulatory framework for combination products which include devices intended to administer medicinal product is laid down in Art. 1 (9) MDR:

“Any device which is intended to administer a medicinal product as defined in point 2 of Article 1 of Directive 2001/83/EC shall be governed by this Regulation, without prejudice to the provisions of that Directive and of Regulation (EC) No 726/2004 with regard to the medicinal product.”

This is the typical situation when the medical device and medicinal substance are not physically combined. They can be co-packaged or separately sold but having cross-references between information of the two products. In these cases, the medical device will need to be CE marked. [51]

The second part of Art. 1 (9) MDR sets out three cumulative conditions that need to be satisfied at the moment of placing on the market by a combination which includes a device intended to administer a medicinal product, to be

considered and regulated as a medicinal product: the device and the medicinal product form a single integral product, it is intended exclusively for use in the given combination, it is not reusable.

“However, if the device intended to administer a medicinal product and the medicinal product are placed on the market in such a way that they form a single integral product which is intended exclusively for use in the given combination and which is not reusable, that single integral product shall be governed by Directive 2001/83/EC or Regulation (EC) No 726/2004, as applicable. In that case, the relevant general safety and performance requirements set out in Annex I to this Regulation shall apply as far as the safety and performance of the device part of the single integral product are concerned.” [51] [54]

New is, that MDR requires for combined products regulated as medicinal products, that Directive 2001/83/EC to be amended.

Therefore, Art. 117 MDR provides an amendment to Annex I to Directive 2001/83/EC point 12 of section 3.2 governing medicinal products for human use, outlining specific requirements for the device component. Previously, there were no clear regulatory requirements for the device element, meaning that many medicinal product manufacturers may not have been aware of actions they needed to take to ensure compliance.

Art. 117 MDR requires that the Marketing Authorisation Application for an integral drug-device combination (referred to in second part of Art. 1 (8) and second part of Art. 1 (9)) should include, where available:

- the results of the assessment of the conformity of the device part with the relevant GSPRs set out in Annex I to MDR contained in the manufacturer's EU declaration of conformity

or

- the relevant certificate issued by a NB allowing the manufacturer to affix a CE marking to the medical device.

Art. 117 MDR, amending Annex I section 3.2 point 12 of Medicinal Product Directive 2001/83/EC, stipulates, if the dossier does not include the results of the conformity assessment referred to above and where for the conformity assessment of the device, if used separately, the involvement of a NB is required, the authority shall require the applicant to provide an opinion on the conformity of the device part with the relevant GSPRs set out in Annex I to MDR issued by a NB designated in accordance with MDR for the type of device in question. [51]

Table 1. Summary of changes for Marketing Authorisations Applications involving integral DDCs [54]

Type of integral device included in the MAA	New submissions as of 26 th May 2020
Class I (sterile, measuring or reusable surgical instrument*), Class IIa, Class IIb, Class III.	The marketing authorization dossier should include a Declaration of Conformity or EU notified body certificate for the medical device, where available. If the above-mentioned documentation is not available, then an opinion** from a notified body must be provided for the medical device.
Class I (non- sterile, non- measuring, or non-reusable surgical instrument)	The marketing authorization dossier should include a Declaration of Conformity for the medical device, where available.
* the reader should note that integral DDC as referred to in second subparagraph of Regulation 2017/745 Art. 1 (9) are not reusable ** opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to Regulation 2017/745	

In supporting the requirements set by Art. 117 MDR, EMA issued the following documents:

- *Questions & Answers on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746)* which provides practical considerations for the MDR implementation, [54] and
- The draft *Guideline on the quality requirements for drug-device combination* which provides guidance on the documentation required in the Quality part (Modul 3 of the CTD dossier) of the medicinal products enclosed in a such combination. This goes into details about the required contents of the marketing authorization dossier. [55]

First above-mentioned document introduces the term “*combination products*” for the medicinal products and medical devices that are placed on the market together, while the second one introduces the term “*Drug-Device Combinations (DDCs)*” for “*medicinal products which contain one or more medical device(s) as an integral part of the composition, as well as medicinal products for which one or more medical device(s) and/or device component(s) are necessary for use of the medicinal product*” and a definition at point 10. Definitions for *Drug-Device Combination Product (DDC)* as follows:

“A medicinal product(s) with integral and/ or non-integral medical device/device component(s) necessary for administration, correct dosing or use of the medicinal product.”

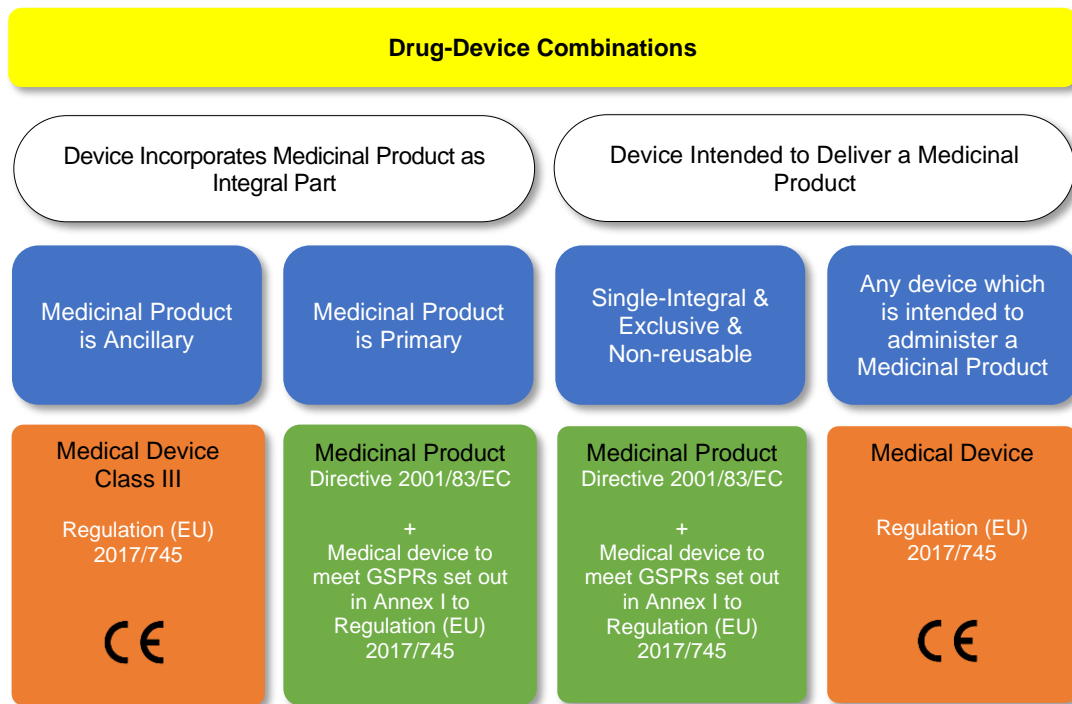


Figure 7 – Drug-device combinations as regulated by MDR [48] [51] [62]

3.6.2. Integral DDCs

Integral DDCs are those combinations under the second sub-paragraphs of both Art. 1 (8) and Art. 1 (9) of the Regulation (EU) 2017/745 on medical devices (the MDR) which are regulated as medicinal products:

- Devices incorporating as an integral part a substance that, if used separately, would be considered a medicinal product *and* the action of the substance is principal, and
- Devices intended to administer a medicinal product where they form a single integral product intended exclusively for use in the given combination which is not reusable. Typically, these devices have measuring, metering or delivery functions.

The assessment procedure for the single integral product is governed by Directive 2001/83/EC or Regulation (EC) No 726/2004, as applicable, however the relevant GSPRs set out in Annex I to MDR shall apply as far as the safety and performance of the device part of the single integral product are concerned.

The CA for the regulation of medicines will evaluate the device specific aspects of safety and performance relevant to the quality, safety and efficacy of the medicinal product while the NB will assess the relevant GSPRs set out in Annex I to MDR.

Examples of medical devices in integral DDCs are:

- Devices for delivery to site of action (e.g. the dropper on the top of the container with eye drops or the mouthpiece on the top of spray cans for throat sprays.)
- Single dose pre-filled syringes, pens and injectors.
- Multi-dose pens and injectors containing a pre-filled cartridge where the cartridge cannot be replaced, and the pen is not designed for subsequent use with a new cartridge.
- Drug-releasing intra-uterine devices; pre-assembled, non-reusable applicators for vaginal tablets.
- Dry powder inhalers that are assembled with the medicinal component and ready for use with single or multiple doses but cannot be refilled when all doses are taken.
- Implants containing medicinal products whose primary purpose is to release the medicinal product.
- Medicinal products with an embedded sensor. [55]

3.6.3. Non-Integral DDCs

“Non-integral DDCs are those DDCs for which the two or more separate components (i.e. medicinal product(s) and device(s)) are not physically integrated during manufacturing but where the medicinal product and the specific device(s) are combined for administration.” [55]

These could be:

- Co-packaged, when the device and the medicinal products are supplied together;
- Sold separately, when the device and the medicinal product are obtained separately, but there are cross-references between information of the two products. The Product Information (SmPC and Leaflet) of the medicinal product should enclose reference to a specific device which to be used for its administration. [55]

Examples of medical devices in non-integral DDCs are:

- Oral administration devices (e.g. cups, spoons, syringes)
- Injection needles and filter needles
- Refillable pens and injectors (e.g. using cartridges)
- Reusable dry powder inhalers; spacers for inhalation sprays
- Nebulisers, vaporisers
- Pumps for medicinal product delivery
- Electronic tablet dispensers [55]

3.6.4. Dossier Requirements for DDCs

As it has been mentioned above in subchapter 3.6.1 Legal stipulations, EMA has released a draft guideline on the quality requirements for drug-device combinations which addresses the new obligations under Art. 117 MDR.

This guideline specifies which information about the device is required to be submitted as part of the marketing authorisation application, when the devices are necessary for the administration, dosing or use of the medicine.

These devices can be integral, co-packaged or referred to in the product information of the medicine but obtained separately. [56]

The guideline also provides with a template for the NB's opinion on the conformity of the device to the relevant general safety and performance requirements laid down in MDR which should be enclosed in MAA, when a CE (Conformité Européenne) certificate or a manufacturer's EU declaration of conformity for the device are not available.

It should be noticed that since the regulatory requirements for the medical device differ depending on whether it is integral or not integral, the specific documentation required to register a DDC slightly differs if the combination is referring to an integral DDC or to a Non-Integral DDC.

The following tables include the specific requirements for a DDC, classified as medicinal product, that should be enclosed in the MAA, as part of the CTD dossier indicated in the draft Guideline on the quality requirements.

Table 2. Specific requirements for integral DDC to be enclosed in Module 1 of the eCTD dossier [55]

Integral DDCs		
MODULE 1 of eCTD format (Vol. 2B Notice to Applicants)		
No.	Title	Further details according to [55]
1.0	Cover Letter	
1.1	Comprehensive table of content	
1.2	Application Form	
1.3	Product Information	
1.3.1	Summary of Product Characteristics, Labelling and Package Leaflet	<p>SmPC</p> <ul style="list-style-type: none"> ● <u>Section 1</u>: The name of the medicinal product should include the device presentation in line with EDQM standard terminology for pharmaceutical form ● <u>Section 4.2</u>: The directions for proper use of the DDC should be described (including cleaning of the device as necessary), in line with relevant guidance. A device tradename may be stated ● <u>Section 6.3</u>: Information on DDC in-use shelf-life should be included, if relevant ● <u>Section 6.4</u>: DDC storage conditions should be listed ● <u>Section 6.5</u>: The type of the device(s) and its (their) component material(s) should be listed ● <u>Section 6.6</u>: Product-specific information should be provided for preparation or handling (including disposal of the device(s)) <p>Package Leaflet</p> <ul style="list-style-type: none"> ● Information should be consistent with the SmPC

		<ul style="list-style-type: none"> ● Instructions on the intended use of the DDC for patients and/or for healthcare professionals (HCP) and be written in such a way as to prevent medication errors ● Information related to the use of the DDC, consistent with the device Instructions for Use (IFU), if applicable, should be included <p>Package leaflet and labels</p> <ul style="list-style-type: none"> ● The outer packaging and the Package Leaflet may only include symbols or pictograms if necessary, to clarify certain information compatible with the SmPC, which may be useful for the patient, to the exclusion of any element of a promotional nature
1.3.2	Mock-up	
1.3.3	Specimen	
1.3.4	Consultation with Target Patient Groups	
1.3.5	Product Information already approved in the Member States	
1.3.6	Braille	
1.4	Information about the Experts	
1.4.1	Quality	
1.4.2	Non-clinical	
1.4.3	Clinical	
1.5	Specific Requirements for different types of applications	
L5. i	Information for bibliographical applications	
1.5.2	Information for Generic, "Hybrid" or Bio-similar Applications	
1.5.3	(Extended) Data/Market Exclusivity	
1.5.4	Exceptional Circumstances	
1.5.5	Conditional Marketing Authorisation	
1.6	Environmental risk assessment	
1.6.1	Non-GMO	
1.6.2	GMO	
1.7	Information relating to Orphan Market Exclusivity	
1.7.1	Similarity	
1.7.2	Market Exclusivity	
1.8	Information relating to Pharmacovigilance	
1.8.1	Pharmacovigilance System	
1.8.2	Risk-management System	
1.9	Information relating to Clinical Trials	

Table 3. Specific requirements for integral DDC to be enclosed in Module 3 of the eCTD dossier [55]

Integral DDCs		
MODULE 3 of eCTD format (Vol. 2B Notice to Applicants)		
No.	Title	Further details according to [55]
3.1	MODULE 3 TABLE OF CONTENTS	
3.2	BODY OF DATA	
3.2.S	DRUG SUBSTANCE	
3.2.S.1	General Information	
3.2.S.1.1	Nomenclature	
3.2.S.1.2	Structure	
3.2.S.1.3	General Properties	
3.2.S.2	Manufacture	
3.2.S.2.1	Manufacturer(s)	
3.2.S.2.2	Description of manufacturing process and process controls	
3.2.S.2.3	Control of materials	
3.2.S.2.4	Controls of critical steps and intermediates	

3.2.S.2.5	Process validation and/or evaluation	
3.2.S.2.6	Manufacturing process development	
3.2.S.3	Characterisation	
3.2.S.3.1	Elucidation of structure and other characteristics	
3.2.S.3.2	Impurities	
3.2.S.4	Control of drug substance	
3.2.S.4.1	Specification	
3.2.S.4.2	Analytical Procedures	
3.2.S.4.3	Validation of analytical procedures	
3.2.S.4.4	Batch analyses	
3.2.S.4.5	Justification of Specification	
3.2.S.5	Reference Standards or Materials	
3.2.S.6	Container Closure System	
3.2.S.7	Stability	
3.2.P	DRUG PRODUCT	
3.2.P.1	Description and composition of the drug product	<ul style="list-style-type: none"> ● Concise information on integral DDCs ● Description and function of each device used with the medicinal product
3.2.P.2	Pharmaceutical Development	<ul style="list-style-type: none"> ● Information relevant to development of the device as integrated into the medicinal product, including the rationale for its selection ● The suitability of the device for its intended use, in the context of the device performing as intended and protecting the medicinal product etc., should be demonstrated ● A clear narrative of device and medicinal product development including all relevant data (e.g. justification of any new device, pharmaceutical form, etc.) should be provided ● The suitability of the DDC and its materials of construction to protect the drug product formulation from light, moisture, microbial contamination and vapour phase permeation (as appropriate) should be confirmed ● Any interactions of the device with the medicinal product should be discussed and justified, as appropriate ● A risk assessment summary for the DDC, aligned with suitable risk assessment principles in ICH Q9 and/or DIN EN ISO 14971
3.2.P.2.1	Components of the drug product (drug substance, excipients)	<ul style="list-style-type: none"> ● A high-level description of the DDC should be provided ● Cross-referring data to the other sections as appropriate
3.2.P.2.2	Drug Product (Formulation Development, Overages, Physiochemical and Biological Properties)	<ul style="list-style-type: none"> ● Considerations related to the intended use of the device and its suitability within the context of the DDC, its therapeutic indication and the relevant target patient population ● Where changes in device design during development occurred, summary bridging data with cross-references to relevant data in Module 4 or Module 5, as appropriate ● Description the impact of any changes in devices during the pivotal clinical trials ● Evaluation and justification of any potential impact of the changes on the quality, safety and efficacy of the medicinal product ● Data to demonstrate and justify the equivalence of the overall performance of the DDC prototype(s) used during pivotal clinical development with the DDC intended for marketing
3.2.P.2.3	<u>Manufacturing Process Development</u>	<ul style="list-style-type: none"> ● A concise description of the DDC manufacturing process development in line with the relevant guidance ● The development, justification and suitability of sterilisation processes of any devices or the DDC should be described ● A comparison of the manufacturing process of DDCs from pivotal or bridging clinical studies to the commercial DDC ● The development of the control strategy for the DDC manufacturing process should be described

3.2.P.2.4	Container Closure System	<ul style="list-style-type: none"> ● Where changes are made to the device, a risk assessment to describe the changes, batches used and trial(s) affected and what mitigation was performed to minimise the impact on product quality <p>Description and rationale for DDC</p> <ul style="list-style-type: none"> ● A brief description of the container closure system should be presented, including the rationale for the container and device component(s) and its (their) materials of construction, including: <ul style="list-style-type: none"> ○ Any non-integral medical devices needed for correct use of the DDC ○ Confirmatory signals for dose delivery (e.g. audible click), sharps injury prevention features, safety/lock-out features to prevent over-dosage, safe disposal information, etc. ○ Information on the matrix and reservoir, including mechanism of drug release ○ Brief details of critical functional components e.g. power supply, dose-setting mechanism, description of controls and alarms and their instructions for use etc. ○ Brief description and rationale for any related technologies e.g. a software application ○ If the device includes a graduation marking, the requirements of Quality of Medicines, should be considered <p>Functional performance aspects of the DDC</p> <ul style="list-style-type: none"> ● The ability of the device to deliver the medicinal product in an accurate and reproducible way should be demonstrated as per the posology stated in Section 4.2 of the SmPC, considering: <ul style="list-style-type: none"> ○ Test conditions should, as far as possible, simulate the use of the DDC under relevant (in-use) storage conditions ○ Consistency of dose delivery should be demonstrated throughout the (in-use) shelf-life of the DDC (e.g. beginning, middle and end) ○ The precision and accuracy of dosing should be guaranteed from release until the end of shelf life and also under special conditions recommended in the SmPC (in-use stability testing) ○ Issues related to usage e.g. shaking, priming, dropping test <p>Compatibility between device and drug product</p> <ul style="list-style-type: none"> ● The physical and chemical compatibility of the drug product with the device(s) should be demonstrated ● Interaction studies (e.g. sorption, precipitation of drug substance in solution, stability, etc.) ● Extractable and leachable studies as appropriate, should be performed ● The suitability of the device for the particular drug product (e.g. considering the rheological properties of the drug product) should be discussed and justified
3.2.P.2.5	Microbiological Attributes	<ul style="list-style-type: none"> ● For sterile products, the integrity of the DDC throughout use and shelf-life, as it relates to preventing microbial contamination should be demonstrated
3.2.P.2.6	Compatibility	
3.2.P.3	Manufacture	
3.2.P.3.1	Manufacturer(s)	<ul style="list-style-type: none"> ● Manufacturer names/addresses for DDC assembly, packaging, sterilisation, labelling and quality control sites, as well as for the EU batch release site(s) should be stated
3.2.P.3.2	Batch formula	

3.2.P.3.3	Description of Manufacturing Process and Process Controls	<ul style="list-style-type: none"> ● Description of any operations that are performed on the device(s) by the DDC manufacturer (such as subassembly steps, washing, coating, sterilisation, or depyrogenation etc.) ● Description of the DDC manufacturer(s) sterilisation methods and conditions for the device(s), where relevant. The sterilisation method(s) used should be validated ● A description of the filling steps and the final assembly of the device(s) into the DDC ● A description of critical process parameters, in-process controls and acceptance criteria ● For applied labels which include printed markings, the position of the label on the container should be specified and acceptable tolerances for the label positioning defined as critical in-process controls (IPCs) in Module 3.2.P.3.3 and Module 3.2.P.3.4
3.2.P.3.4	Controls of critical steps and intermediates	<ul style="list-style-type: none"> ● Any critical steps should be justified ● Any device-specific intermediates should be defined ● Relevant specifications, test methods and their validation should be provided ● Any holding times should be defined and justified
3.2.P.3.5	Process validation and / or evaluation	Process validation for the manufacture of the DDC should be performed in line with relevant European guidelines, including the assembly and sterilisation of the device(s) (if applicable) and any filling steps
3.2.P.4	Control of excipients	
3.2.P.4.1	Specifications	
3.2.P.4.2	Analytical procedures	
3.2.P.4.3	Validation of analytical procedures	
3.2.P.4.4	Justification of specifications	
3.2.P.4.5	Excipients of human or animal origin	
3.2.P.4.6	Novel Excipients (<i>et to A 3</i>)	
3.2.P.5	Control of drug product	
3.2.P.5.1	Specification(s)	<ul style="list-style-type: none"> ● Description of DDC appearance ● Performance tests relevant to the intended use of the DDC e.g. extractable volume, delivered dose uniformity and functionality of the device at both release and shelf life ● Other critical test parameters related to CQAs of the medicinal product, e.g. glide force, needle penetration force, seal integrity, delivery time, exposed needle length after activation of device (needle penetration depth, relevant to route of administration), activation force, transdermal adhesion properties, lock-out system control to prevent over-dosing and signals to confirm dose delivery to the patient/user
3.2.P.5.2	Analytical Procedures	
3.2.P.5.3	Validation of Analytical Procedures	
3.2.P.5.4	Batch analyses	
3.2.P.5.5	Characterisation of Impurities	
3.2.P.5.6	Justification of specification(s)	
3.2.P.6	Reference Standards or Materials	
3.2.P.7	Container Closure System	<ul style="list-style-type: none"> ● A description of the container closure system, including the materials of construction of each primary packaging and device component and its specification ● Information on sites and processes for sterilisation and/or subassembly of device(s) in line with the EMA Sterilisation guideline (EMA/CHMP/CVMP/QWP/BWP/850374/2015) or the NB Certificate of Conformity, where a sterile CE-marked device is used ● Suitable quality control specifications of medical device(s) and/or device components ● Detailed specifications and test procedures (including description, identification and functional tests as relevant), as well as critical dimensions, technical drawings and photographs of primary and functional secondary packaging materials

		<ul style="list-style-type: none"> Evidence of compliance with the relevant Ph. Eur. monographs, if applicable, and/or food contact Directives, as appropriate (such as declarations of compliance from suppliers)
3.2.P.8	Stability	<ul style="list-style-type: none"> Functionality tests (e.g. dose delivery per actuation, syringe ability, communication with software, etc.) In case of complex DDCs, such as integral ingestible devices, additional functional tests related to the intended use of the medicinal product are required In-use stability testing performed under the conditions of use as stated in the SmPC, unless otherwise justified Microbial quality, sterility, content/potency and purity for the entire shelf-life and in-use period, as appropriate Simulated transport studies that encompass chemical (e.g. degradation) and physical (e.g. vibration) stability, where relevant
3.2.A	APPENDICES	
3.2.A.1	Facilities and Equipment	
3.2.A.2	Adventitious Agents Safety Evaluation	<p>TSE agents</p> <ul style="list-style-type: none"> TSE statement confirming compliance of the component(s) of the DDC with EMEA/410/01 rev.3, to the European Standard “Medical devices utilising animal tissues and their derivatives – part 3 (EN ISO 22442-3:2007)” and Ph. Eur. 5.2.8 “Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products” <p>Viral safety</p> <ul style="list-style-type: none"> An assessment of the risk to the DDC with respect to potential viral contamination in accordance with the European Standard “Medical devices utilizing animal tissues and their derivatives – part 3 (EN ISO 395 22442-1:2015)” and Ph. Eur. 5.1.7 Viral safety For substances from human blood/plasma, compliance with relevant EU directives (the Blood directive 2002/98/EC and its associated technical directives), Ph. Eur. and EMA guidelines should be verified <p>Other adventitious agents</p> <ul style="list-style-type: none"> Detailed information regarding other adventitious agents, such as bacteria, mycoplasma and fungi should be provided in relevant sections pertaining to the device within the core dossier, as appropriate
3.2.A.3	Novel Excipients	
3.2.R	REGIONAL	<ul style="list-style-type: none"> Information related to demonstration of compliance of the device(s) with Annex 1 to MDR (i.e. the applicable GSPRs) Cross-reference to studies or additional information provided in 3.2.P sections, if relevant
3.2.R.1	REGIONAL INFORMATION	<ul style="list-style-type: none"> EU Declaration of Conformity issued by the device manufacturer or Certificate of Conformity issued by a NB that allows a CE mark to be displayed on the device or The applicant's confirmation that the device part meets the relevant GSPRs if the device is a class I device (excluding Im, Is, Irsi) or NB opinion on the conformity of the device with the relevant GSPRs, issued by an appropriately designated NB III if the device is a class Im, Is, Irsi, IIa, IIb <p>Notified Body Opinion (NBOp)</p> <ul style="list-style-type: none"> it is recommended that the NBOp is presented as a technical summary report as in the Annex 3 and Annex 4 [55], which provide guidance on the type of data to be included in the NBOp and propose a template to harmonise its format <p>Usability (human factor) Studies</p> <ul style="list-style-type: none"> A usability study – to evaluate whether the DDC can be used safely to deliver the medicinal product to the target population - is expected

		<ul style="list-style-type: none"> ● A usability study summary should be presented with cross-referencing details in Modul 5 ● Published and/or other relevant data for identical/similar devices on the market ● Applicants are encouraged to follow/use relevant harmonised standards to demonstrate compliance such as IEC 62366-1:2015 and IEC/TR 62366-2:2016 <p>Platform technology/technologies</p> <ul style="list-style-type: none"> ● A summary of the (relevant) data for those aspects of the device which pertain to the 'platform' should be presented ● Suitability with regards to specific products and subsets of the target patient population should be demonstrated ● Reference to previously approved DDC(s) developed and marketed by the marketing authorisation holder (MAH) may be included as supportive information, as well as other relevant quality aspects in support of the proposed approach
3.2.R.2	METHODS VALIDATION PACKAG	
3.3	LITERATURE REFERENCES	-

Table 4. Specific requirements for non-integral DDC to be enclosed in Module 1 of the eCTD dossier [55]

Non-Integral DDCs		
MODULE 1 of eCTD format (Vol. 2B Notice to Applicants)		
No.	Title	Further details according to [55]
1.0	Cover Letter	
1.1	Comprehensive table of content	
1.2	Application Form	
1.3	Product Information	
1.3.1	Summary of Product Characteristics, Labelling and Package Leaflet	<p>SmPC</p> <ul style="list-style-type: none"> ● <u>Section 4.2:</u> The directions for proper use of the DDC should be described (including cleaning of the device as necessary), in line with relevant guidance. A device tradename may be stated ● <u>Section 6.3:</u> Information on DDC in-use shelf-life should be included, if relevant ● <u>Section 6.4:</u> DDC storage conditions should be listed ● <u>Section 6.5:</u> The type of the device(s) and its (their) component material(s) should be listed ● <u>Section 6.6:</u> Product-specific information should be provided for preparation or handling (including disposal of the device(s)) <p>Package Leaflet</p> <ul style="list-style-type: none"> ● Information should be consistent with the SmPC ● Instructions on the intended use of the DDC for patients and/or for healthcare professionals (HCP) and be written in such a way as to prevent medication errors ● Information related to the use of the device, consistent with the device IFU, if applicable, should be included <p>Package leaflet and labels</p> <ul style="list-style-type: none"> ● The outer packaging and the Package Leaflet may only include symbols or pictograms if necessary, to clarify certain information compatible with the SmPC, which may be useful for the patient, to the exclusion of any element of a promotional nature
1.3.2	Mock-up	
1.3.3	Specimen	
1.3.4	Consultation with Target Patient Groups	
1.3.5	Product Information already approved in the Member States	
1.3.6	Braille	
1.4	Information about the Experts	
1.4.1	Quality	

1.4.2	Non-clinical	
1.4.3	Clinical	
1.5	Specific Requirements for different types of applications	
L5. i	Information for bibliographical applications	
1.5.2	Information for Generic, "Hybrid" or Bio-similar Applications	
1.5.3	(Extended) Data/Market Exclusivity	
1.5.4	Exceptional Circumstances	
1.5.5	Conditional Marketing Authorisation	
1.6	Environmental risk assessment	
1.6.1	Non-GMO	
1.6.2	GMO	
1.7	Information relating to Orphan Market Exclusivity	
1.7.1	Similarity	
1.7.2	Market Exclusivity	
1.8	Information relating to Pharmacovigilance	
1.8.1	Pharmacovigilance System	
1.8.2	Risk-management System	
1.9	Information relating to Clinical Trials	

Table 5. Specific requirements for non-integral DDC to be enclosed in Module 3 of the eCTD dossier [55]

Non-Integral DDCs		
MODULE 3 of eCTD format (Vol. 2B Notice to Applicants)		
No.	Title	Further details according to [55]
3.2.P	DRUG PRODUCT	
3.2.P.1	Description and composition of the drug product	<ul style="list-style-type: none"> Description and function of any device used to administer the DDC
3.2.P.2	Pharmaceutical Development	<ul style="list-style-type: none"> Summary of relevant Quality information for the device including safety and performance, in the context of the device reproducibly delivering the required dose of the medicinal product within the intended use Evidence for the suitability of the device(s) in its (their) intended use, provide a clear narrative of device and medicinal product development, and provide all relevant data Information should reflect the risk of the device to impact the quality, safety and/or efficacy of the medicinal product A brief description of the device, and of the functionality of the device, together with the medicinal product
3.2.P.2.1	Components of the drug product (drug substance, excipients)	<ul style="list-style-type: none"> A high-level description of the DDC should be provided
3.2.P.2.2	Drug Product (Formulation Development, Overages, Physicochemical and Biological Properties)	<ul style="list-style-type: none"> A general discussion on the choice of device should be provided, including the intended use (usability), rationale for choice of device The functional aspects of the device should be qualified in line with its complexity and should include the rationale for the choice and optimisation of the design and performance (such as dose-delivery performance and mechanical functionality of the device) Dose accuracy/delivered dose uniformity should be demonstrated with the intended medicinal product Any markings/graduation should be justified in line with the posology stated in Section 4.2 of the SmPC Details of the cleaning of the device(s) should be stated, where relevant
3.2.P.2.3	<u>Manufacturing Process Development</u>	
3.2.P.2.4	Container Closure System	

3.2.P.2.5	Microbiological Attributes	<ul style="list-style-type: none"> For medicinal products intended to be used sterile, the sterility of the non-integral device should be verified (e.g. by reference to the CE certificate) Maintenance of sterility throughout use and shelf-life of the final medicinal product should also be demonstrated
3.2.P.2.6	Compatibility	<ul style="list-style-type: none"> Compatibility should be considered from an in-use stability perspective and the physical and chemical compatibility of the drug product with the device(s) should be demonstrated (e.g. sorption, precipitation of drug substance in solution, stability, etc.) Interaction studies should be performed, as appropriate, using a risk-based approach All materials in contact with the drug product should be considered The suitability of the device for the particular drug product (e.g. considering the rheological properties of the product) should be discussed and justified
3.2.P.3	Manufacture	
3.2.P.3.1	Manufacturer(s)	
3.2.P.3.2	Batch formula	
3.2.P.3.3	Description of Manufacturing Process and Process Controls	
3.2.P.3.4	Controls of critical steps and intermediates	
3.2.P.3.5	Process validation and / or evaluation	
3.2.P.4	Control of excipients	
3.2.P.4.1	Specifications	
3.2.P.4.2	Analytical procedures	
3.2.P.4.3	Validation of analytical procedures	
3.2.P.4.4	Justification of specifications	
3.2.P.4.5	Excipients of human or animal origin	
3.2.P.4.6	Novel Excipients (<i>et to A 3</i>)	
3.2.P.5	Control of drug product	
3.2.P.5.1	Specification(s)	
3.2.P.5.2	Analytical Procedures	
3.2.P.5.3	Validation of Analytical Procedures	
3.2.P.5.4	Batch analyses	
3.2.P.5.5	Characterisation of Impurities	
3.2.P.5.6	Justification of specification(s)	
3.2.P.6	Reference Standards or Materials	
3.2.P.7	Container Closure System	
3.2.P.8	Stability	<ul style="list-style-type: none"> In-use stability data should be provided for the drug product in contact with the device, including device functionality that may impact the quality, safety and/or efficacy of the medicinal product
3.2.A	APPENDICES	
3.2.A.1	Facilities and Equipment	
3.2.A.2	Adventitious Agents Safety Evaluation	<p><u>If self-declared</u></p> <p>TSE agents</p> <ul style="list-style-type: none"> TSE statement confirming compliance of the component(s) of the DDC with EMEA/410/01 rev.3, to the European Standard “Medical devices utilising animal tissues and their derivatives – part 3 (EN ISO 22442-3:2007)” and Ph. Eur. 5.2.8 “Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products” should be provided <p>Viral safety</p> <ul style="list-style-type: none"> An assessment of the risk to the DDC with respect to potential viral contamination in accordance with the European Standard “Medical devices utilizing animal tissues and their derivatives – part 3 (EN ISO 395 22442-1:2015)” and Ph. Eur. 5.1.7 Viral safety For substances from human blood/plasma, compliance with relevant EU directives (the Blood directive 397 2002/98/EC and its associated technical directives), Ph. Eur. and EMA guidelines should be verified

		<p>Other adventitious agents Detailed information regarding other adventitious agents, such as bacteria, mycoplasma and fungi should be provided in relevant sections pertaining to the device within the core dossier, as appropriate</p> <p>Otherwise</p> <ul style="list-style-type: none"> ● A valid NB Certificate of Conformity can be accepted as evidence of compliance with EU requirements
3.2.A.3	Novel Excipients	
3.2.R	REGIONAL	<ul style="list-style-type: none"> ● Information related to demonstration of compliance of the device(s) with Annex 1 to MDR (i.e. the applicable GSPRs) ● Cross-reference to studies or additional information provided in 3.2.P sections, if relevant
3.2.R.1	REGIONAL INFORMATION	<ul style="list-style-type: none"> ● An index should be provided, which should cross refer to studies or information provided in 3.2.P sections as appropriate ● EU Declaration of Conformity issued by the device manufacturer, as evidence of the CE-mark ● NB Certificate of Conformity for devices of risk classes above Class I (i.e. Im, Is, Irsi, IIa, IIb and III) ● Any changes implemented in the design of the device during the development of the medicinal product should be discussed in terms of the impact on product performance characteristics (e.g. delivered dose, needle penetration force for subcutaneous/intramuscular injection and other usability factors) ● Appropriate data to demonstrate and justify the similarity of the overall performance during clinical phases with that after approval ● Summary bridging data with cross-reference to relevant data in Module 4 or Module 5, as appropriate, where required and applicable (e.g. owing to changes in device design) ● Where (device) clinical investigations were incorporated into the pivotal DDC clinical trial, the rationale for this approach should be discussed and justified in Module 5 <p><u>Usability data</u></p> <ul style="list-style-type: none"> ● A usability study - that the device/medicinal product can be used safely to deliver the required dose to the target population – is expected ● Published or other relevant data for identical/similar devices on the market ● A formal usability study is required, if usability cannot be satisfactorily demonstrated in this way ● A summary cross-referring to Module 5 ● Discussion of, and justification for the use of platform devices
<u>3.2.R.2</u>	METHODS VALIDATION PACKAG	
3.3	LITERATURE REFERENCES	-

4. Discussions

4.1. Canada

In Canada there are specific designated legislative provisions for DDCs, stipulated in a Policy, consisting of the document on Drug/Device Combination Products [25] and of the document on Drug/Medical Device Combination Product – Decisions [26]. The Policy was created with the purpose to ensure that patients have timely access to drug-medical device combination products by establishing a single window approach and a more efficient submission processing system. However, this Policy, presented in chapter 2.4.1. of this thesis, provides an interim mechanism to address a gap in the current regulatory schemes for drugs and medical devices. Ultimately, it will be necessary to amend the *Food and Drugs Act* and / or the *Food and Drug Regulations* and / or the *Medical Device Regulations* to provide an appropriate regulatory framework for new and emerging therapeutic products that are difficult to define under current frameworks, including combination products. [25]

The Policy on drug-device combinations does not cover all types of drug-medical device combinations, but only those that meet the definition provisions, namely, the combination where a drug component and a device component form a singular integrated product with therapeutic action. Subsequently, this entire product will be registered either as a medicinal product or as a medical device. The Policy documents do not address those combinations, where the drug component and the device component are either sold separately or as a kit or separate in one packaging, and to be combined only when used by the patient or other users. In these later cases each component should be regulated under its specific regulations.

In Canadian legislation the key for the distinction between medicinal product (drug) and medical device lies in the interpretation of the main concepts that define them: therapeutic effect and mechanism of action. Medical devices and medicinal products share the common essence of having a therapeutic effect, while they differ by the mechanism of action to reach the intended effect.

Although the Policy mentions as distinctive elements in the favour of medicinal part, *the pharmacological, immunological, or metabolic means*, it should be also considered the term “chemical means”, which was lately added in the Food and Drug Act and also mentioned in the Guidance Document: Classification of Products at the (Medical) Device-Drug Interface. [27] Concerning the definitions for pharmacological, immunological and

metabolic the Guidance document repeats in a footnote the definitions as laid down in Drug/Medical Device Combination Products Policy document. [25] But just as document [25] does not provide a definition of “chemical means”, neither does guideline [27] defines this term. However, despite the three definitions given, their content is often disputed between manufacturers of, in particular, substance-based medical devices and the authorities, so that the absence of a definition of chemical means is not really significant in the author’s view.

The author of this thesis recommends the manufacturers, to consider these premises in early stages of a development of a drug-device combination, because the necessary regulatory requirements for compiling the submission dossier are different in case of the combination will follow a pathway specific for a device or for a medicinal product.

The challenges for a manufacturer / sponsor occur when the distinction between devices and drugs is not clear, and they should follow a procedural process to get the appropriate classification.

Once the classification is established by the Therapeutic Products Classification Committee, the combination product will be regulated either under Food and Drug Regulations if it is classified as a drug or under Medical Devices Regulations if it is classified as a device.

No guidelines interpreting and detailing the requirements stipulated in both regulations mentioned above are existing and the Acts also give no further details requirements for these specific products.

To give a further recommendation for combination products registered as devices, the manufacturer should be aware that their QMS should be approved through the MDSAP programme, as in Canada this condition became mandatory after 1st January 2019.

4.2. The European Union

According to the explanations given in chapter 3 of this thesis, there is no specific legislative document in EU, like the two Policy documents in Canada, to regulate drug-device combinations, but these have been addressed under the Art. 1 (3) and Art. 1 (4) of the Directive 93/42/EEC and in Art. 1 (8) and Art. 1 (9) in connection with Art. 117 of the Regulation (EU) 2017/745 from the perspective of the medical devices. Therefore, their approach and assessment are based on the way by which a medical device is put into service and placed on the market with a medicinal component (substance or product), considering the follow possibilities:

- Where the device is intended to administer a medicinal product and it is either
 - separately obtained and marketed together (co-packaged)

- separately obtained and marketed, but with crossed-referred information
- form a single integral product
- Where the device incorporates as an integral part a medicinal substance

The Draft Guideline on quality requirements for drug-device combinations provided by EMA [55] explains in the opinion of the author an understandable way the concepts of “*Drug-Device Combinations (DDCs)*”, “*Integral DDCs*” and “*Non-integral DDCs*” including a lot of examples (see subchapter 3.6.2. and 3.6.3. of this thesis). Although, this document is not legally binding, these terms continue to be loosely used without a legal definition, so the experience of the author.

It is important to notice that integral DDCs falling within the definition of Art. 1 (9) MDR are the primary focus of the Guideline on the quality requirements for drug-device combinations, while the DDCs falling within the definition of Art. 1 (8) MDR will likely become more commonplace as technology develops. For the last ones, it is recommended to follow the basic principles defined in the guideline and to consult with a competent authority when certain elements may not be applicable.

Having studied the requirements laid down in MDD and MDR by the author, both legislations have a similar approach in regard to combination products. The stipulation in Art. 1 (8) MDR is in so far equivalent to Art. 1 (4) MDD and both sub paragraphs of Art. 1 (9) MDR are more or less equivalent to Art. 1 (3) MDD.

Integral drug-device combination products are assessed and regulated based on the greatest contribution to the therapeutic effect and registered either as a medical device or a medicinal product (see the first versus the second paragraph in Art. 1 (8) MDR and the second paragraph in Art. 1 (9) MDR). In cases of the integral DDCs which have to be regulated as medicinal products, the above mentioned EMA guideline on the quality requirements for DDCs [55] lays down in very detail the quality requirements to be submitted as part of a MAA. In the author's opinion, this can lead to the fact that the authorities always want to see this rigid schema (see Tables 2 – 5 in this thesis) and that previously existing flexibilities adapted to the respective product will be lost in the future.

In both cases when a DDC product is regulated either under pharmaceutical or medical device law, the core concept always is that the NBs will assess whether the devices meet the relevant GSPR including a possible interaction between drug and device, while the CAs for the regulation of medicines will evaluate the device`s specific aspects of safety and performance relevant to the quality, safety and efficacy of the medicinal products part.

The Marketing Authorisation Application for integral DDCs, submitted as of 26 May 2020, must comply with all these requirements, but not legal guidance is available at this time. EMA issued only a Draft Guideline on quality requirements and a list of Questions and Answers on implementation of Art. 117 MDR requirements. Currently authorized medicinal products with an integral medical device will not be impacted by Art. 117 MDR as it is not intended to be applied retrospectively to integral DDCs already authorised or to those MAAs that have been submitted prior to 26 May 2020. However, if any substantial change to the design or intended purpose of the device component occurs, or a new device is introduced after the marketing authorisation has been granted, any necessary certificate/ declaration of conformity/ NB opinion should be submitted as part of the variation/ extension application, as appropriate, to EMA or NCA (Question #2.6. of [54]).

Even if the involvement of the NB is required, this is not defined in the context of DDC change types in EMA variations procedures. As such, given the fact that the current EU variations classification guideline EC 1234/2008 [57] does not adequately address changes to the device constituent of an integral DDC, pharmaceutical industry is looking for guidance as to manage these changes. In this context, European Federation of Pharmaceuticals Industries and Associations (EFPIA) "*would like clarifications with regards to the translation of DDC change types in EMA variation procedures (Type IA, IB and II)*". [58]

This requirement is mentioned in a Reflection Paper developed by the EFPIA-MQEG/ GMP Working Group on Drug-Device Combinations (DDC) – "An Industry Perspective About Quality Management System (QMS) for Drug-Device Combination Products". [58] The document defines a pharmaceutical industry perspective on the relationship between MDR and the Pharmaceutical Quality System (PQS) as set in the so-called GMP rules Chapter I and in other PQS documents such as ICH Q10 and 21 CFR (US-FDA). Its aim is to clarify and enable the implementation of MDR requirements for QMS by pharmaceutical industry and raises a series of points for clarification and promote harmonisation of QMS requirements for designing, developing, manufacturing and marketing DDC products in Europe. Moreover, this comprehensive paper poses many questions and also suggests solutions and tasks to be performed in the event that a pharmaceutical company manufactures and distributes DDCs but is not the legal manufacturer of the medical device part in the combination.

It is well understood that DDCs with the main purpose on the medicinal product part are to be authorised and marketed as medicinal products in compliance in particular with Art. 117 MDR and Annex I – GSPR. However, it is not clear, not only for the author, which other requirements set under other Articles of the MDR would or would not apply to the device when combined with a medicinal product like an integral or non-integral combination apart of those related to affix the CE marking. This question is

pertinent mainly for the MDR Articles defining requirements for labelling, distribution, traceability and post-marketing surveillance. As mentioned, document [58] formulates questions on the various requirements of the MDR (laid down in its articles and annexes) as to whether or to what extent the pharmaceutical company must also meet or take these into account.

The author states that only the tightening of the requirements of Art. 117 MDR for the DCCs addressed there allows the pharmaceutical industry to make these considerations, although the products have already been marketed under the MDD.

5. Summary and Conclusions

A comparative overview of the drug-device combination products in the two world regions discussed in this thesis, is summarized in the table below:

Table 6. Comparative overview concerning regulation of DDC products in Canada and the European Union (presentation by the author)

Crt.	Canada	The European Union
Def.	<ul style="list-style-type: none"> • Clear definitions for DDCPs, only in Policy 	<ul style="list-style-type: none"> • No legal definitions for DDCPs, only in Guideline
Legal Framework	<ul style="list-style-type: none"> • Food and Drug Act • Food and Drug Regulation • Medical Devices Regulations • Drug/Medical Device Combination Products Policy • Policy on Drug/Medical Device Combination Products – Decisions 	<ul style="list-style-type: none"> • MDD (only applicable during a transitional phase) • MDR • MEDDEV 2.1/3 rev. 3 (part: consultation procedure) • EMA's Q&A on MDR's implementation • Draft Guideline on quality requirements issued by EMA
Authorities	<ul style="list-style-type: none"> • Health Canada <ul style="list-style-type: none"> ◦ HPFB <ul style="list-style-type: none"> ▪ TPD ▪ BGTD ▪ MDD 	<ul style="list-style-type: none"> • No specific designated European Authority • NB • National CA or EMA
Judgement	<p style="text-align: center;">DDCP</p> <p style="text-align: center;">↙ ↘</p> <p>Medicinal ← PMA → Medical Product Device</p>	<p style="text-align: center;">DDCP</p> <p style="text-align: center;">↙ ↘</p> <p>Medicinal ← Therapeutic → Medical Product Effect Device</p>
Considerations	<ul style="list-style-type: none"> • The entire combination should have: <ul style="list-style-type: none"> ◦ a therapeutic action ◦ both components integrated in a single product ◦ both components in line with acceptable standards of safety, efficacy and quality 	<ul style="list-style-type: none"> • Intended use of the device in combination • Placing of the two components on the market / Putting them into service • Not reusable condition for device • Action of medicinal substance (ancillary or principal)

Crt.	Canada	The European Union
Challenges	<ul style="list-style-type: none"> • Classification of the combination as a drug or device • Early classification in case of new development 	<ul style="list-style-type: none"> • Consultation procedure • Information exchange between NB and CA/EMA • NB has to take due account on CA`s/EMA`s opinion • Assessment of the medical device part in the context of MAA • NB has to provide an opinion

Both Canada and the European Union have a similar approach to regulate drug-device combination products. This was possible after Canada has amended its regulation on DDCs in that way that the regulatory requirements in Canada are harmonized both with FDA and EU requirements and would assist in the development of mutual recognition agreements (MRA) with those jurisdictions.

The author of this thesis supports the rapid preparation of such an MRA so that a DDC that is marketable in the European Union is also marketable in Canada without further applications and vice versa.

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Annexes

Annex 1

(taken from guideline MEDDEV 2.1/3 rev.3) [47]

Documentation to be provided by the Notified Body to the Competent Authority for the ancillary medicinal substance or the ancillary human blood derivative as incorporated in the medical device:

1) General information

A general description of the medical device including the manufacturer's claim regarding the purpose of the incorporation of the ancillary medicinal substance or the ancillary human blood derivative, together with a critical appraisal of the results of the risk assessment.

2) Quality Documentation

- Qualitative and quantitative particulars of the constituents

A description of the ancillary medicinal substance or the ancillary human blood derivative, and the amount (giving a range where appropriate) of the ancillary medicinal substance or the ancillary human blood derivative incorporated into each medical device. If the medicinal substance or the ancillary human blood derivative is modified during its incorporation into the medical device, relevant information shall be provided.

- Description of method of manufacture

An overall description will already form part of the application to the Notified Body; the section dealing with incorporation of the ancillary medicinal substance or the ancillary human blood derivative in the medical device should be provided.

- Controls of starting materials
The specification for the ancillary medicinal substance or the ancillary human blood derivative shall be provided.
- Control tests carried out at intermediate stages of the manufacturing process of the medical device
This information is only necessary if it is directly relevant to the quality of the ancillary medicinal substance or the ancillary human blood derivative as incorporated in the medical device.
- Final Control tests of the ancillary medicinal substance or the ancillary human blood derivative in the medical device
Qualitative and quantitative tests carried out to control the ancillary medicinal substance or the ancillary human blood derivative incorporated in the medical device.

- **Stability**
Information defined to show the ancillary medicinal substance or the ancillary human blood derivative maintains its desired function throughout the defined shelf-life of the medical device including, taking account of the manufacturer's recommended storage conditions, potential interaction with other materials, and potential degradation of the ancillary medicinal substance or the ancillary human blood derivative.

3) Non-clinical Documentation

- **Non-clinical pharmacology**
 - **Pharmacodynamics**
This section should address the intended action of the ancillary medicinal substance or the ancillary human blood derivative in the context of its incorporation into a medical device.
 - **Pharmacokinetics**
It is anticipated that pharmacokinetic studies will not be required in the majority of cases. Some or all of the following areas may need to be addressed as appropriate:
 - Description of the pattern of local and systemic exposure to the ancillary medicinal substance or to the ancillary human blood derivative, - Where the level of exposure fluctuates (AUC), the maximum level and duration of exposure should be considered,
 - Where it is considered possible that potential levels of systemic exposure may present a safety concern, maximum peak plasma concentration should be established, taking due consideration of individual variability,
 - New active substances will require information on the release from the medical device, and, if relevant, its subsequent absorption, distribution, metabolism and excretion (AUC and eventually metabolites, if relevant).
 - **Toxicity (including single-dose toxicity, repeat-dose toxicity, genotoxicity, carcino-genicity and reproductive and developmental toxicity, as applicable).**
Reference to the known toxicological profile of the ancillary medicinal substance or the ancillary human blood derivative may be provided. In the case of new active substances, the results of toxicity tests should be provided, taking into account relevant CHMP guidelines. [59] This may include information on toxicity and biocompatibility of the medical device which may be available from evaluation in accordance with the EN 10993 series of standards.
 - **Local tolerance** This is of particular relevance since the route of exposure to the ancillary medicinal substance or the ancillary human blood derivative may be different from its conventional application. The relevant results of medical device testing according

to EN ISO 10993 should be provided or, where appropriate, information from the scientific literature.

4) Clinical evaluation

Since these medical devices will be class III, clinical data will form part of the information provided to the Notified Body under annex II or III of the applicable Directive. This data will address the requirements for clinical evaluation of the medical device incorporating an ancillary medicinal substance or an ancillary human blood derivative as required by Annex X of Directive 93/42/EEC or annex VII of Directive 90/385/EEC, respectively. This data will address the safety of the medical device in its entirety. The usefulness of the ancillary medicinal substance or the ancillary human blood derivative incorporated in the medical device should be addressed by clinical evaluation or by cross-reference to other sections of the dossier, as applicable.

An appropriate methodology for clinical investigations on medical devices is described in EN ISO 14155-1:2003 - Clinical investigation of medical devices for human subjects - Part 1: General requirements and EN ISO 14155-2:2003 - Clinical investigation of medical devices for human subjects - Part 2: Clinical investigation plans.

Particular attention shall be given to any specific guidelines (e.g. EMEA guideline on the clinical and non-clinical evaluation during the consultation procedure on medicinal substances contained in drug eluting (medicinal substance-eluting) coronary stents, MEDDEV guidance 2.7.1 Appendix 1 – clinical evaluation of coronary stents).

5) Labelling

Details supplied by the manufacturer of labelling or information to be provided with the medical device with regard to the ancillary medicinal substance or the ancillary human blood derivative, is to be supplied to the Competent Authority to assist in the understanding of the safety and usefulness of the ancillary medicinal substance or the ancillary human blood derivative together with the medical device.

Annex 2

(taken from EMA recommendation on the procedural aspects and dossier requirements for the consultation to the European Medicines Agency by a notified body on an ancillary medicinal substance or an ancillary human blood derivative incorporated in a medical device or active implantable medical device) [48]

Data requirements and format of the application dossier**Section 1 comprises**

- Application form
- General information of the medical device
 - General description of the medical device
 - Appendix 2 (Scientific explanation that the action of the medicinal substance or human blood derivative incorporated in the medical device is only ancillary to that of the device in line with the MEDDEV guidance 2.1/3 rev 3, December 2009)
- Signed declaration and CV from a qualified expert(s)²
- Report from the notified body verifying the usefulness of the incorporation of the ancillary medicinal substance / ancillary blood derivative in the medical device
- Labelling

Section 2 comprises

- Module 2.3: quality overall summary (relevant parts) for the ancillary medicinal substance or ancillary human blood derivative itself in accordance with the format of Volume 2B, CTD of the notice to applicants (EudraLex, The rules governing medicinal products in the European Union).
- Critical summaries (or expert reports) of the quality, non-clinical and clinical data provided in line with MEDDEV guidance 2.1/3 rev 3,

² When expert reports are used in Section 2 as critical summaries of the documentation, we request a signed declaration of ownership of the report. The expert shall have suitable technical or professional qualifications. A CV of the expert including brief information on their educational background, training and occupational experience shall be included. The professional relationship of the expert to the medical device manufacturer/notified body shall be declared.

December 2009 for the ancillary medicinal substance or the ancillary human blood derivative incorporated in the medical device. (i.e. critical summaries (or expert reports) of points 2b), 3) and 4) as detailed in Section C.3 of the MEDDEV guidance 2.1/3 rev 3, December 2009)

Section 3 comprises

- CTD Module 3: relevant parts, for ancillary medicinal substance or ancillary human blood derivative itself, in accordance with the format of Volume 2B, CTD of the notice to applicants (EudraLex, The rules governing medicinal products in the European Union).

Note: For non-biological ancillary medicinal substances for which an Active Substance Master File (ASMF) or a Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP) is used, refer to the European Medicines Agency guideline on ASMF (EMA/CVMP/134/02 Rev 1; CPMP/QWP/227/02 Rev 1).

Note: For ancillary human blood derivatives for which a PMF already exists, the relevant information in module 3 already submitted as part of the PMF does not need to be provided with the application dossier for the consultation procedure. In this case, a notification letter should accompany module 3 from the medical device manufacturer including the following:

1. Reference to the PMF number and date of the certification
2. Declaration that the PMF certificate, evaluation report and PMF dossier are fully applicable for the ancillary human blood derivative
3. Declaration that the PMF holder has submitted the PMF certificate, evaluation report and PMF dossier to the medical device manufacturer

State that the PMF certificate, evaluation report and PMF dossier are available at the European Medicines Agency, and therefore not attached to this notification letter. However, on request, the PMF dossier will be sent to the European Medicines Agency within 48 hours

- Quality documentation following the headings and data requirements of Section C.3 point 2b) of the MEDDEV guidance 2.1/3 rev 3, December 2009 for the ancillary medicinal substance or the ancillary human blood derivative incorporated in the medical device.

Section 4 comprises

- Non-clinical documentation following the headings and data requirements of Section C.3 point 3 of the MEDDEV guidance 2.1/3 rev 3, December 2009 for the ancillary medicinal substance or the ancillary human blood derivative incorporated in the medical device.

Section 5 comprises

- Clinical documentation following the headings and data requirements of Section C.3 point 4 of the MEDDEV guidance 2.1/3 rev 3, December 2009 for the ancillary medicinal substance or the ancillary human blood derivative incorporated in the medical device.

Useful guidelines to fulfil the data requirements

The following list of guidelines is not exhaustive and there may be other respective further guidelines applicable.

1. **General guidance**

- MEDDEV guidance 2.1/3 rev 3, December 2009 relating to the application of the Council Directive 90/385/EEC on active implantable medical devices and the Council Directive 93/42/EEC on medical devices.
- EudraLex Notice to Applicants Volume 2B (Presentation and content of the dossier – CTD).
- Guideline on active substance Master File procedure (EMA/CVMP/134/02 Rev 1; CPMP/QWP/227/02 Rev 1). Please note this guideline is not applicable for biological active substances.

2. **Guidance for blood derivatives**

Quality

- Note for guidance on Plasma-derived medicinal products (EMA/CHMP/BWP/706271/2010).
- Guideline on the scientific data requirements for a Plasma Master File (PMF) (EMA/CPMP/BWP/3794/03 Rev 1).
- Note for guidance on virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses (CPMP/BWP/268/95).
- Relevant European Pharmacopoeia monographs.
- Guideline on the investigation of manufacturing processes for Plasma-derived medicinal products with regard to vCJD Risk (CPMP/BWP/5136/03).
- CHMP position statement on Creutzfeldt-Jacob disease and Plasma-derived and Urine-derived medicinal products. (CHMP/BWP/303353/2010)

Good manufacturing practice

- Manufacture of medicinal products derived from human blood or plasma, Annex 14 to the EU Guide to good manufacturing practice.

Non-clinical and clinical safety

- CPMP/CHMP³ guidance on medicinal blood products from the Blood Products Working Party (BPWP) ([http://www.ema.europa.eu - Regulatory/human medicines/scientific guidelines/clinical efficacy and safety/ blood products](http://www.ema.europa.eu - Regulatory/human%20medicines/scientific%20guidelines/clinical%20efficacy%20and%20safety/blood%20products)).

3. Guidance for biological/biotechnology products**Quality**

- Relevant CPMP/CHMP Guidelines published on the European Medicines Agency website ([http://www.ema.europa.eu - Regulatory/human medicines/scientific guidelines/biologicals](http://www.ema.europa.eu - Regulatory/human%20medicines/scientific%20guidelines/biologicals)).
- Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products ([EMEA/410/01 Rev 3](#)).

Good manufacturing practice

- Manufacture of biological medicinal products for human use, Annex 2 to the EU Guide to good manufacturing practice.

Non-clinical and clinical safety

- Relevant CPMP/CHMP guidance on biological/biotechnological products from the Safety Working Party (SWP) and CHMP temporary working parties ([http://www.ema.europa.eu - Regulatory/human medicines/scientific guidelines/non-clinical](http://www.ema.europa.eu - Regulatory/human%20medicines/scientific%20guidelines/non-clinical)) & ([http://www.ema.europa.eu - Regulatory/human medicines/scientific guidelines/clinical efficacy and safety](http://www.ema.europa.eu - Regulatory/human%20medicines/scientific%20guidelines/clinical%20efficacy%20and%20safety)).

4. Guidance for new chemical entities**Quality**

- Relevant CPMP/CHMP Guidelines published on the European Medicines Agency website ([http://www.ema.europa.eu - Regulatory/human medicines/scientific guidelines/clinical efficacy and safety/quality](http://www.ema.europa.eu - Regulatory/human%20medicines/scientific%20guidelines/clinical%20efficacy%20and%20safety/quality)).

Good manufacturing practice:

- Relevant Annexes to the EU Guide to good manufacturing practice.

Non-clinical and clinical safety

- Relevant CPMP/CHMP guidance on new chemical entities from the Safety Working Party (SWP) and Efficacy Working Party (EWP) and CHMP temporary working parties ([http://www.ema.europa.eu - Regulatory/human medicines/scientific guidelines/non-clinical](http://www.ema.europa.eu - Regulatory/human%20medicines/scientific%20guidelines/non-clinical)) &

³ The Committee on Proprietary Medicinal Products (CPMP) changed its name to Committee for Medicinal Products for Human Use (CHMP) on 1 May 2004.

(<http://www.ema.europa.eu> - Regulatory/human medicines/scientific guidelines/clinical efficacy and safety).

- Guideline on the clinical and non-clinical evaluation during the consultation procedure on medicinal substances contained in drug-eluting (medicinal substance-eluting) coronary stents (EMA/CHMP/EWP/110540/2007).

Annex 3

Annex 1: Proposal for Notified Body Opinion template *(taken from EMA Guideline on the quality requirements for DDCs) [55]*

NB logo
NB name and address
NB number

Notified Body Opinion

(Article 117 of the Medical Device Regulation (EU 2017/745))

Compliance of device(s) incorporated into an integral drug-device
combination product
with

Annex I (General Safety and Performance Requirements)
Medical Device Regulation (EU 2017/745)

Administrative reference number: _____
(including version number)

Reviewer name and position: _____

NB authorisation (signature): _____

Authorisation date (YYYY/MM/DD) _____

I. SUMMARY OF NOTIFIED BODY OPINION

<Clearly state opinion i.e. acceptable or not acceptable>

<Include a brief summary highlighting the basis of the opinion, with any relevant constraints or other considerations>

II. LIST OF ABBREVIATIONS

<Insert list of abbreviations>

III. ASSESSMENT OF THE GENERAL SAFETY AND PERFORMANCE REQUIREMENTS (GSPR)

a. Basis of assessment, Article 117 of Regulation EU 2017/745.

In consideration of the following text from Article 117 of the Medical Device Regulation (EU 2017/745), [sic]... "Where, if the dossier does not include the results of the conformity assessment referred to in the first subparagraph and where for the conformity assessment of the device, if used separately, the involvement of a notified body is required in accordance with Regulation (EU) 2017/745, the authority shall require the applicant to provide an opinion on the conformity of the device part with the relevant general safety and performance requirements (GSPR) set out in Annex I to that Regulation issued by a notified body designated in accordance with that Regulation for the type of device in question."

b. General Drug-Device Combination product information.

<Summary information to ensure mutual understanding of the product under assessment including a detailed description of product, in particular the device component(s) indications, method of administration, intended use, etc.>

c. Scope of assessment

<List of applicable GSPRs, with justification for any omissions>

d. Assessment

<This should form the main body of the report>

<For each applicable GSPR, summarise the data presented, and final outcome(s) of the assessment>

<Any changes made to the device during pivotal clinical trials should be described (changes, timelines) and the impact on relevant GSPRs discussed>

e. Notified Body Opinion

<Clearly state the opinion and a summary of the justification for the NB opinion>

IV. REFERENCES

<List relevant references, including ISO standards>

Annex 4

Annex 2: Template cover sheet for Notified Body Opinion*(taken from EMA Guideline on the quality requirements for DDCs) [55]*

It is intended that this document is completed in two situations:

1. Where an application is made for a stand-alone medicinal product. In this case, the MAH completes this section.
2. Where an application is made that utilises a platform technology. In this case, it is the technology owner who completes this section, effectively providing a letter of authorisation to the MAH to use the data, similar to the approach used where a CEP holder authorises the use of the active substance in an EU procedure.

GENERAL INFORMATION

PRODUCT DETAILS	
Invented / Trade name of the medicinal product	<as per MAA>
Applicant	<Name and address of MAH i.e. legal entity holding the MA>
Marketing authorisation type	<e.g. Centralised application>
Marketing authorisation procedure number	<e.g.>
Pharmaco-therapeutic group (ATC code)	<e.g. D08A C52>
Indication(s)	<As per SPC4.1>
Pharmaceutical form(s) and strength(s)	<e.g. 10mg, 20mg INN solution for injection, pre-filled syringe>
INN (or common name) of the active substance(s):	<as per MAA>
Authorisation to use NBOp	<Suitably authorised / signed by either the MAH, applicant or the platform technology holder>

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Olguta Stanescu