Health Canada Santé Canada

# Issue Identification Paper

## Drug-Device Combination Products (DDCPs)

## Draft for Consultation

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## Objective

This paper is intended to identify the key challenges associated with Health Canada's oversight of drug-device combination products (DDCPs) as per Health Canada's Policy on Drug/Medical Device Combination Products[1] (the Policy). DDCPs are health products that combine drugs and medical devices as a single entity. For the purposes of this paper, a drug is considered to be a pharmaceutical, radiopharmaceutical, natural health product (NHP), biologic, cell, tissue, organ, gene therapy, or human blood and its components.

## Background

Health Canada is authorized under the *Food and Drugs Act* (the Act) to regulate the safety, efficacy and quality of health products. The current regulatory frameworks for drugs and medical devices are suitable for the assessment of separate categories of products. However, these frameworks were not designed to address products that combine drugs and medical devices as single entities.

Health Canada employs the Policy when classifying and assessing these products for use in clinical trials and for market authorization. Under the Policy, which was first adopted in 1997 and last substantially updated in 1999[2], a DDCP is authorized for the Canadian market under a single regulatory pathway. Although the current version of the Policy continues to be used for the classification and risk management of DDCPs, industry stakeholders have indicated that the Policy could benefit from greater clarity and expanded detail.

The Act was amended in 2014 to include a definition of "therapeutic product" that encompasses "a drug or device or any combination of drugs and devices, but does not include a natural health product within the meaning of the Natural Health Products Regulations." However, at present, there are no provisions specific to DDCPs in any of the regulatory frameworks for drugs and devices.

In 2019, new authorities to address Advanced Therapeutic Products (ATPs) were added to the Act. ATPs are drugs or devices whose complex nature or use presents significant challenges to their oversight under the current frameworks. The ATP authorities provide Health Canada with the ability to authorize a product or group of products under the Act by creating a regulatory scheme that is separate from, yet informed in part by, existing regulations. A DDCP could be considered as a candidate for the ATP pathway if its characteristics were such that the current regulatory requirements for the drug and device components were determined by Health Canada to be insufficient and/or unsuitable.

## Issue identification

The convergence of medicines and medical technologies has produced a wide range of physically combined drugs and medical devices that vary in nature from the relatively simple to the highly sophisticated. While these products offer enhanced health benefits to patients, their diversity and complexity has created challenges for regulators who must:

1) Classify DDCPs;

2) Determine an appropriate single regulatory pathway; and

3) Establish suitable pre- and post-authorization requirements.

These challenges have also created issues of clarity and transparency for sponsors and manufacturers seeking to market a DDCP in Canada.

### 1. Classifying drug-device combination products

The Policy uses the term "combination product" to describe a drug-device combination product. However, this term is also used in the regulatory environment to describe drug-drug combinations consisting of two integrated drug components that may or may not belong to the same subcategory. Common examples of these types of products are pharmaceutical-pharmaceutical, pharmaceutical-biologic, and pharmaceutical-NHP combinations. To avoid confusion and where possible, this paper explicitly differentiates DDCPs from the broader term of "combination product".

The Policy defines a "combination product" as:

> "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."

Health Canada's interpretation of this definition determines the scope of products to which the Policy will apply. However, the Policy does not provide an interpretation of this definition. A comprehensive discussion of what is meant by "integrated in a singular product" is required to determine when a therapy that combines a drug and device can be classified as a DDCP. For example, the Policy requires greater clarification as to why some co-packaged drugs and devices meet the definition of a "combination product", whereas others do not and require separate authorizations for the drug and device components.

The Policy also does not provide examples of drugs and devices used in combination that were either classified or not classified by Health Canada as DDCPs. Some examples of previous decisions regarding the principal mechanism of action (PMOA) are provided in the document Policy on Drug/ Medical Device Combination Products- Decisions.[3] However, the inclusion of examples in an updated policy document would better support Health Canada's interpretation of the DDCP definition. For consideration, examples of these are provided in the following subsections.

#### 1.1 Products classified as DDCPs

A DDCP consists of two or more integrated components, of which at least one component is a drug and at least one is a medical device. Health Canada classifies each individual component as either a drug or a device, based on the respective definitions in the Act and assisted by using the factors outlined in the Health Canada guidance document on Classification of Products at the (Medical) Device-Drug Interface[4].

Examples of products that Health Canada has classified as DDCPs include drug delivery systems, drug-enhanced devices, and device-enhanced drugs.

**Drug delivery systems**

In a drug delivery system, the drug and device components are combined to provide a single therapeutic effect in which the device component functions solely as the delivery vehicle for the drug component. A drug delivery system may be:

- **Combined at time of manufacture**

  This type of drug delivery system contains at least one drug and device component that are physically integrated at the time of manufacture. Examples include pre-filled syringes, transdermal drug patches, and drug-eluting disks.

- **Co-packaged and combined prior to administration of the drug**

  In these drug delivery systems, the components are manufactured separately, co-packaged, and combined prior to administration. Co-packaged drug delivery systems classified by Health Canada as DDCPs include metered dose inhalers, as well as internal creams and their applicators.

**Drug-enhanced devices**

In a drug-enhanced device, the drug and device components are each intended to produce their own therapeutic effect. The device also functions as a drug delivery vehicle. Some common examples of drug-enhanced devices are drug-eluting stents, drug-coated surgical sutures, and antibiotic-coated catheters. Advances in the field of tissue engineering have resulted in products of even greater complexity, such as bioresorbable cell-scaffolds, that could be argued to fall under the definition of a combination product. The drug and device components in these products tend to be less distinct than in DDCPs containing small molecule drugs, which makes it more difficult for Health Canada to classify these products.

**Device-enhanced drugs**

The emergence of digital medication has produced a new class of DDCP, the device-enhanced drug. One example involves a solid oral drug product embedded with an ingestible event marker (IEM) sensor. This integrated combination of drug and device is part of a larger system used to monitor patient adherence to a medication regimen. In a device-enhanced drug, the drug component is the primary component.

### 1.2 Products not classified as DDCPs

An updated policy document should also include examples of other drugs and devices used in combination that Health Canada does not classify as DDCPs.

- **Kits**

  A kit consists of two or more health products that are contained in one package for convenience purposes but are not required to be combined prior to administration or use. The products are often separately licensed. As such, the Policy does not apply.

- **Cross-labelled products**

With cross-labelled products, the drug and device components are individually authorized and sold separately but are labelled to be used together exclusively. The respective labelling for each product cross-references the other product(s) for either concurrent or successive administration. Since these products are not integrated in a singular entity, the Policy does not apply.

- **Companion diagnostics**

Companion diagnostics are medical devices that provide an analytical output to help determine whether a certain drug therapy might be beneficial or detrimental to a specific patient or patient subset. Health Canada does not apply the Policy to these products since the drug and device components are not integrated in a singular product.

- **Veterinary combination products**

The MDR define a "medical device" as a device within the meaning of the *Food & Drugs Act*, but does not include a device that is intended for use in relation to animals. Devices intended for use in or on animals are regulated under the *Food & Drug Regulations* and, consequently, veterinary drug-device combinations are not subject to the Policy.

- **Equipment used for point-of-care manufacturing of drugs**

Equipment used to process raw materials whereby the output is a pharmaceutical, biologic, or NHP do not meet the current definition of combination product and as such, the Policy is not applied. Examples include 3D printers of drugs, cell sorters, and equipment used to transduce cells with viral vectors.

## 2. Determining the regulatory pathway for drug-device combination products

### 2.1 A single regulatory pathway

Prior to the 1997 Policy, Canadian manufacturers were required to apply for separate clinical trial and/or market authorizations under both the *Food & Drug Regulations* (F&DR) and the *Medical Devices Regulations* (MDR). This practice complicated the risk/benefit assessment of these products by separating the reviews of the respective components rather than supporting an evaluation of the entire product. In addition, some manufacturers raised concerns that the regulatory burden for this approach created a disincentive to seek clinical trial or market authorizations for their products in Canada.

The 1997 Policy was created to provide a single regulatory pathway to authorize the entire combination product. This Policy was intended to streamline the review of these products without compromising the health and safety of Canadians.

### 2.2 Principal mechanism of action

According to the Policy, in order to apply a single authorization scheme for a DDCP, Health Canada must first determine the PMOA. The PMOA is the mechanism by which the primary effect of a DDCP is achieved. The product is then subject to either the F&DR or the MDR, according to the following classification rules set out in section 5 of the Policy:

- 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 F&DR, 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 MDR.
- 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 MDR.

Although written to include all drugs under the Act, the Policy has not been updated to include the *Natural Health Products Regulations* (NHPR), which were promulgated in 2004. Health Canada has since used the Policy to authorize DDCPs under the NHPR in cases where the primary component is a natural health product. However, the lack of mention of the NHPR in the Policy could create confusion for manufacturers of DDCPs involving natural health products.

The Policy does not elaborate on how one should determine the PMOA. Establishing the PMOA is self-evident with DDCPs that function solely as drug delivery systems: the drug component is primary. However, for drug-enhanced devices, there is more than one therapeutic effect and the component that provides the most significant effect may not be immediately apparent.

The Policy also does not advise on how to compare the components when there are two or more effects of similar therapeutic importance. The Policy's focus on the "claimed effect or purpose" suggests that only the efficacy/effectiveness of the drug and device components should be considered when determining the PMOA. It is unclear if the relative risk posed by each component should also be taken into account. That is, if one component presents a greater risk than the other component, the Policy offers no direction on whether this should influence designation of the PMOA.

Health Canada has established through practice that when a drug-enhanced device consists of a Class I device combined with a drug, the DDCP is authorized under the drug pathway. This is because Class I devices require no pre-market licence application. However, when a drug-enhanced device involves a device component of a higher risk class, additional clarity is needed for classifying the primary component.

Finally, the classification approach based solely on the PMOA may have created misconceptions for some stakeholders about how a non-combined drug or a device is classified. Some stakeholders have inferred from the PMOA rules that mechanism of action is also the sole determinant when classifying a non-combined product at the device-drug interface. This is incorrect, as there are several additional factors also considered in these decisions.[5]

### 2.3 Reconsideration of classification decisions

The Policy states that it "will not be 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." External stakeholders have criticized this wording as being vague since it does not specify if the reclassification would be day-forward or retroactive.

## 3. Requirements for drug-device combination products

### 3.1 Standards of evidence for product authorization

Health Canada implemented the Policy to enable an appropriate level of oversight of the two or more components in a DDCP, both separately and combined, without creating unnecessary burden for the manufacturer. This is evident in section 5(4) of the Policy:

> "Although a combination product will be subject to either the *Food and Drug Regulations* or the *Medical Devices Regulations*, both the principal and ancillary components shall meet acceptable standards of safety, efficacy and quality."

The standards of evidence to confirm the safety, efficacy/effectiveness and quality of the primary and ancillary components are not elaborated in the Policy nor are they set out in supporting guidance documents. This could create challenges for stakeholders when preparing a submission package for both clinical trial and market authorization.

Some operational challenges have been encountered in cases where the classification of a DDCP doesn't align with the risk presented by the product. One example is a drug-eluting balloon used for below-the-knee treatment. This is a drug-enhanced device in which a Class II device is the primary component. With Class II devices, manufacturers are not required to submit supporting data to Health Canada for the primary nor ancillary components unless requested. Consequently, this evidence must often be requested by Health Canada after a manufacturer has applied for a device licence, which creates delays in reviewing the respective components.

Risk Management Plans (RMPs), although not yet required by regulation, are currently requested by policy for drugs only. Further consideration is required with respect to the application of RMPs to a DDCP when the ancillary component is a drug.

### 3.2 Labelling requirements

At present, Health Canada applies labelling requirements to only the primary component of a DDCP. For example, a DDCP authorized under the F&DR would need to comply with only the labelling requirements for drugs. There are however some differences in the labelling requirements for drugs, natural health products and medical devices. These differences are accentuated with the application of a single authorization pathway.

Sections C.01.003 through C.01.013 of the F&DR describe requirements for the inner (product container) and outer (product package) labels. Additionally, a Product Monograph in accordance with the Terms of Market Authorization must accompany a Notice of Compliance for a New Drug Submission (NDS), an Abbreviated New Drug Submission (ANDS) or a Supplemental NDS or ANDS.

Labelling and packaging requirements for natural health products are described in Part 5 (sections 86-98) of the NHPR. Similar labelling requirements are imposed on NHPs under the NHPR as with drugs under the F&DR; however, there is no requirement for an NHP to have an accompanying Product Monograph.

General labelling requirements for medical devices, as stipulated in sections 21 through 23 of the MDR, are also similar to those for drugs but are less extensive. While the MDR requires labelling to include storage conditions and expiration dates, there are no requirements for devices to have quantitative lists of medicinal ingredients nor qualitative lists of non-medicinal ingredients. Information on how to achieve the optimum performance of the device, as well as adverse effects, contraindications, cautions and warnings, is provided in the Instructions For Use (IFU). However, unlike the Product Monograph, there is no standardized format to be followed for medical devices IFU.

The extent of information to be provided for the ancillary component of a DDCP is not articulated in guidance documents for either the Product Monograph or the Device IFU. As a result, the respective documents often emphasize information relating to the safety and efficacy/effectiveness of the primary component.

The requirements for Plain Language Labelling apply only to drugs regulated under F&DR. Natural health products and medical devices are currently exempt from these additional labelling requirements. This also creates a regulatory gap that depends on whether or not the drug component is the primary component in a DDCP.

Similarly, since Risk Management Plans are currently applicable only to drugs, it is unclear how additional labelling requirements to mitigate risk under an RMP might be applied to a drug that is the ancillary component in a DDCP.

### 3.3 Quality assurance standards

Quality assurance standards are required to ensure the consistent production and control of drugs and medical devices. However, there are differences in the respective standards for drugs and devices, which affect the regulation of DDCPs.

Compliance with Good Manufacturing Practices (GMP) standards is required for Canadian market authorization of a drug product. Either a drug establishment licence (DEL) under the F&DR, or a natural health product site licence (SL) under the NHPR confirms these quality standards.

Prior to issuing a DEL for a manufacturing facility, Health Canada must verify that the activities comply with GMP, as per Part C, Division 2 of the *Food and Drug Regulations*. Verification is achieved through inspections conducted by Health Canada or through use of an inspection report prepared by an international partner under the Pharmaceutical Inspection Co-operation Scheme.

A site inspection is not required prior to pre-market authorization of a natural health product.

A medical device license is required for all Class II, III, and IV devices prior to their marketing in Canada. While the specific authorization prerequisites vary for Class II, III and IV devices, all three classes are required to satisfy the National Standard of Canada CAN/CSA-ISO 13485:2016, Medical Devices — Quality Management Systems — Requirements for Regulatory Purposes. The ISO standard outlines specific requirements for establishing a Quality Management System (QMS). In Canada, a manufacturer must obtain certification of QMS using a third party auditor under the Medical Device Single Audit Program (MDSAP).

A comparison of the medical device ISO certification requirements and the drug GMP requirements indicate considerable overlap in the areas of Equipment, Sanitation, Manufacturing Procedures, Quality Control, Finished Product Testing, and Records Retention. The ISO standard, however, has no comparative requirement in the areas of Raw Material Testing and Stability.

The current framework for a DDCP requires that a sponsor comply with either the GMP or QMS standards when the primary component is considered to be, respectively, a drug or a device. Evidence of GMP or QMS compliance for the ancillary component of a DDCP is not required. This has created challenges for Health Canada when considering the classification of co-packaged drugs and devices. Specifically, packaging requirements under GMP apply only to the direct packaging of a drug and do not as a rule extend to the co-packaged device components that deliver a drug. This results in different GMP requirements for single-entity drug-delivery systems that are combined at time of manufacture, and co-packaged drug delivery systems that are combined prior to administration. As an example, the packaging requirements for a pre-filled applicator includes testing of the device component, since it also functions as the product packaging. In contrast, there are no packaging requirements under GMP for an applicator that is co-packaged with a drug component.

Most DDCPs regulated under the F&DR are also required to demonstrate compliance with Good Manufacturing Practices for the manufacture of Active Pharmaceutical Ingredients (APIs).[6] This requirement is currently not applied to APIs in DDCPs where the primary component is a medical device and the product is licensed under the MDR.

### 3.4 Post-authorization safety reporting and quality surveillance

Several challenges have been identified with regard to safety reporting of DDCPs, which affect reporters and Health Canada.

There are potential complications with reporting an adverse drug reaction (ADR) or a medical device incident (MDI) in connection with a DDCP. The single pathway under which a DDCP is authorized, although clear to a manufacturer, is often not apparent to healthcare professionals or patients. The duplicate reporting of an event, through both drug and device reporting processes at Health Canada, is also a possibility. It may also be a challenge for a reporter to determine whether an adverse event is associated with the drug or the device component.

Since a DDCP is authorized for market according to its primary component, it is difficult for Health Canada to track and respond to safety issues associated with the ancillary component. When an ADR or MDI involves the ancillary component, the report submitted to Health Canada, which is based on the primary component, may not contain the most relevant information. A sufficient amount of data to evaluate the risk presented by the ancillary component may not be provided. As a result, the timeliness of Health Canada's signal assessment and risk mitigation measures can be affected. Risk communication measures involving the ancillary component of a DDCP are also complicated if there is insufficient product identification information available.

DDCPs are also subject to only one quality inspection regime, which is associated with the primary component. When a DDCP is authorized under the MDR, Health Canada may encounter challenges when there are issues involving the ancillary component. As an example, if there is an issue involving the quality of an active pharmaceutical ingredient (API) used in the drug component, the absence of a DEL makes it difficult to link the API to the DDCP.

## 4. Next steps

Following the publication of this issue identification paper, Health Canada will proceed with its analysis of the key considerations for updating its approach to classifying and regulating drug-device combination products. The comments received through the posting of this paper will further inform this analysis.

## 5. How to get involved

Health Canada is seeking your input to confirm whether all of the issues relating to Health Canada's classification and oversight of DDCPs have been sufficiently captured in this paper. This consultation is open for a 60-day comment period starting May 10, 2021.

You are encouraged to submit your comments to

Bureau of Policy, Science and International Programs
Therapeutic Products Directorate
hc.policy.bureau.enquiries.sc@canada.ca

## Appendix 1

**Current definitions of drug and device**

Section 2 of the *Food and Drugs Act* defines the terms drug and device as follows:

**Drug**

"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."

**Device**

"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."

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[1] *Policy on Drug Medical Device Combination Products,* March 1, 2006. Health Canada. http://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/policies/drug-medical-device-combination-products.html

[2] The Policy was revised in 2006 for administrative purposes. No substantial changes were made to its content.

[3] Policy on Drug/Medical Device Combination Products- Decisions. July 21, 2014. Health Canada.

[4] Guidance Document: Classification of Products at the (Medical) Device-Drug Interface. February 7, 2018. Health Canada. http://www.canada.ca/en/health-canada/services/drugs-health-products/classification-health-products-device-drug-interface/guidance-document-factors-influencing-classification-products-device-drug-interface.html

[5] Guidance Document: Classification of Products at the (Medical) Device-Drug Interface. February 7, 2018. Health Canada. http://www.canada.ca/en/health-canada/services/drugs-health-products/classification-health-products-device-drug-interface/guidance-document-factors-influencing-classification-products-device-drug-interface.html

[6] Good Manufacturing Practices (GMP) Guidelines for Active Pharmaceutical Ingredients (API) - (GUI-0104). November 8, 2013. https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/drugs/guidelines-active-pharmaceutical-ingredients-0104.html#s3