Combination Products Coalition

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VIA EMAIL

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Bureau of Policy, Science and International Programs
Therapeutic Products Directorate
Health Canada
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Re: Issue Identification Paper: Drug-Device Combination Products (DDCPs) Draft for Consultation

Dear Sir or Madam:

The Combination Products Coalition (CPC)[1] welcomes the opportunity to offer comments on Health Canada's Drug-Device Combination Products (DDCPs) Issue Identification Paper. The CPC is particularly pleased and encouraged to see the effort Health Canada is making to address the uniquely complex and challenging oversight required for drug-device combination products under Health Canada's Policy on Drug/Medical Device Combination Products (the "Policy").

CPC supports Health Canada maintaining much of its Policy, which CPC acknowledges has worked well, particularly regarding drug delivery systems. Additionally, CPC believes global harmonization of certain standards for DDCPs across jurisdictions would be highly appreciated, as alignment would expedite access to innovative treatments for patients. Due to the complexity associated with regulating DDCPs, CPC believes that adoption of mature combination product regulatory schemes—such as that from U.S. Food and Drug Administration (FDA)—would be beneficial in accomplishing such alignment and would better position Canada to partake in global clinical trial opportunities related to innovative drug-device combination therapies. CPC also recommends considering a streamlined approach to minimize regulatory burdens associated with certain products, such as kits, as has been implemented in the U.S., due to the differences in the regulatory and legal constructs for each market. Given the number of permutations of combination products, CPC also encourages Health Canada to be very clear in the guidance documents it issues, particularly with respect to submission requirements, the timing of submissions, and supporting documentation.

On behalf of CPC, CPC's International Working Group submits the following compilation of CPC members' comments and suggested revisions for Health Canada's consideration.

[1] The CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in combination product issues. One of our top priorities is to work collaboratively with regulatory agencies on issues affecting combination products to advance our common mission: providing the best possible health care to patients. Our diverse, cross-industry membership permits the CPC to bring a special, broad and unique perspective to these issues. For more information on the CPC, please visit our website: http://combinationproducts.com.

Section	Comments	Proposed Revision/Suggestions
Objective		
	• While CPC acknowledges Health Canada's desire to distinguish combination products that include a device and a drug from Health Canada's broader definition of "combination products" that include combinations of two or more components of the same type, CPC believes the use of the term "DDCP," regardless of which component provides the primary mode of action (PMOA), might increase confusion within the industry. For example, draft guidance from the European Medicines Agency (EMA) uses the term "drug-device combination" for products where the drug is the PMOA only for: 1. Devices that when placed on the market or put into service incorporate, as an integral part, a substance that, if used separately, would be considered as a medicinal product, provided that the action of the substance is principal[2] 2. Devices intended to administer a medicinal product, where they form a single integral product intended exclusively for use in the given combination and which is not reusable.[3] Typically, these devices have measuring, metering or delivery functions. • CPC further encourages Health Canada to clearly define what Health Canada considers to be a "combination product." The use of the term "combination product" does not align with its provided definition consistently throughout the Issue Identification Paper. For example, the Issue Identification Paper seems to refer to a physically combined/single entity as a "combination product" then later refers to this combination as co-packaging while implying co-labelled products are out of scope of the "combination product" definition. CPC supports the adoption of a clear definition.	• Align combination product classifications with other major regulatory jurisdictions to enable sponsors to comply with pre- and post-authorization requirements. • Clearly define what Health Canada considers to be a "combination product" and consider adopting the definition from ASTM (when published). • Remove natural health products (NHPs) due to an entirely different pathway and evidence applicable to such products.
Background		
	• CPC encourages Health Canada to ensure it makes clear to sponsors when the DDCP pathway can be used and when complex DDCPs should be filed via the ATP pathway. • The Issue Identification Paper appears to use terms, such as "integrated" and "combined" interchangeably when discussing DDCP.	• Define terms to make clear when a term has the same or different meaning within the context of the regulatory framework.

[2] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on Medical Devices, art. 1(8), 2017 O.J. (L 117) 14.
[3] *Id.* at art. 1(9).

Section	Comments	Proposed Revision/Suggestions
1. Classifying drug-device combination products		

1.1 Products classified as DDCPs	• CPC seeks further clarity regarding what Health Canada considers to be “necessary” to the use of a drug (e.g. syringes).
	• CPC seeks clarification regarding whether or not the combination at the time of manufacture or later affects its evaluation. For example, oral syringes—which are technically co-packaged but are combined prior to administration—are currently not considered DDCPs. CPC seeks clarification regarding whether this example would be considered a “kit.”
	• CPC believes the proposed categories of DDCPs could result in unnecessary confusion with regard to regulatory identities and how DDCPs would be regulated in Canada. Specifically:
	  ○ As a matter of current practice, many drugs and locally provided devices are “combined prior to administration of the drug.” For example, a commercially available, commonly used syringe may be locally supplied and used by healthcare professionals to deliver a drug in a clinic. The drug and device licenses may be held by different sponsors. The approach to categorize the combined use of the drug and device as a "combination product" would result in unnecessary regulatory burden and hinder patients’ access to medicines.
	  ○ According to the Issue Identification Paper, "drug-enhanced devices" also "[function] as a drug delivery vehicle." In this context, the distinction between "drug delivery systems" and "drug-enhanced devices" is not clear. CPC urges Health Canada to articulate the relevance of these categories from a marketing application and evidentiary standard perspective. For example, if a combination product has a drug and device as its components but the device has a software component in addition to its hardware component, CPC seeks clarification on whether the software would be considered while reporting issues to Health Canada if there is a defect in the Software component that causes an issue administering a drug.
	• Due to the existence of a "combination product" pathway pursuant to Canada’s 1997 Policy, CPC supports adoption of FDA’s regulatory interpretations of (a)"single entity" and "co-packaged" combination products, and (b) PMOA as the criteria for the determination of the type of regulatory application and primary review authority. CPC believes this proposed approach addresses the intentions of the "drug delivery systems," "drug-enhanced devices," and "device-enhanced drugs" approach.
		• Utilize the PMOA to determine the type of regulatory application and primary review authority.
		• Adopt the FDA’s regulatory interpretations of (a) "single entity" and "co-packaged" combination products, and (b) PMOA as the criteria for the determination of the type of regulatory application and primary review authority.
		• Provide additional co-packaging clarification with specific examples to describe component co-packaging configurations that would or would not be classified as DDCP.

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	• CPC also encourages Health Canada to provide clear reporting requirements that align with other common reporting models, such as the models used by the FDA, EU Medical Devices Regulation (MDR), or Japan Pharmaceuticals and Medical Devices Agency.	
1.2 Products not classified as DDCPs	***Kits*** • CPC recommends streamlining regulatory requirements associated with "kits." • CPC seeks clarification regarding Health Canada's interpretation of "required" versus "not required" in its definition of a "kit." For example, CPC seeks guidance on determining when it might be considered "convenience" if the drug must be administered via IV/SQ applications that requires a syringe. CPC encourages Health Canada to consider adopting a streamlined approach to minimize regulatory burdens associated with some products, such as kits (e.g. co-packaged combination products), similar to the United States, which was adopted due to differences in the regulatory and legal constructs for each market. ***Cross-Labelled Products*** • CPC does not recommend specifically including so-called "cross-labelled" products within an updated policy. Such policies, used in the U.S., have generated significant regulatory uncertainty, as described by CPC in a recent position paper.[4] • However, if Health Canada elects to include "cross-labelled" products within the definition of combination products, the CPC recommends a narrow and clear definition to avoid ambiguity and related issues regarding the classification of different types of products that may (but do not necessarily have to) be used together. The CPC notes that there is an international harmonization effort for defining combination products ongoing through ASTM International[5] (committee E55), and the coalition recommends aligning with such an effort, particularly on the subject of "cross-labelled" products. • Similarly, CPC seeks clarity on the term "exclusively" within the "cross-labelled product" definition. Specifically, CPC would appreciate clarification regarding whether both the drug and device components must be mutually exclusive, or if one component may allow wider use, noting that the coalition prefers a narrow definition limited to such "mutually exclusive" use. • If such products are in scope, the CPC encourages Health Canada to issue guidance regarding documentation for separate	• Align across different health authorities and regulatory authorities. • Issue guidance regarding documentation for separate drug and device submissions to address issues such as cross-references to other dossier(s) and the timing of review, among others.

[4] COMBINATION PRODUCTS COALITION, PROPOSED CROSS-LABELING/COMBINED USE GUIDANCE CONSIDERATIONS (2020), http://combinationproducts.com/wp-content/uploads/2020/09/CPC-CL-WG-Proposed-Cross-Labeling-Guidance-Considerations-Aug-2020.pdf.

[5] *See* Cicely Enright, *The Right Combination*, ASTM INTERNATIONAL (July/August 2020), https://sn.astm.org/?q=features/right-combination-ja20.html.

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	drug and device submissions that addresses issues such as cross-references to other dossier(s) and the timing of review, among others. • If such products are in scope, the CPC also encourages Health Canada to provide safety reporting requirements for "cross-labelled" products to clarify expectations for each product independently and together, similar to the U.S. FDA's regulation[6] and guidance[7] on post-market safety reporting.	
2. Determining the regulatory pathway for drug-device combination products		
2.1 A single regulatory pathway	• CPC supports adoption of a single regulatory pathway based on PMOA. For drug-device synergies that cannot be easily discerned, CPC suggests having two branches of the European Union Medical Device Regulation then converging the processes back to a single pathway. If Health Canada adopts such a framework, CPC suggests that Health Canada address "co-packaged" products, and provide guidance on the pathway for DDCP versus the path for the constituent parts, and what is required for DDCP when the drug and device manufacturer differ.	• Adopt a single regulatory pathway approach for "single entity" and "co-packaged" combination products based on PMOA.
2.2 Principal mechanism of action	• CPC seeks evaluation of the pre- and post- authorization requirements for drug effectiveness monitoring apps. Based on the mechanism of action, Software as a Medical Device (SaMD) must already follow the MDR.	• Consider the impact on SaMDs' classification within the scope of this guidance. CPC encourages Health Canada to issue a separate Issue Identification Paper on the matter.
3. Requirements for drug-device combination products		
3.1 Standards of evidence for product authorization	• CPC agrees with the issues Health Canada highlights regarding Class II devices. Such devices are essentially "label review only," and, unlike drugs, are not required to show evidence of efficacy and validation, among other requirements. • CPC supports aligning Risk Management Plans (RMPs), a new requirement for devices, with the RMP requirement for drugs. CPC believes a single review pathway for RMPs will be holistic and pragmatic.	• Ensure the policy clearly sets forth data and expectations so sponsors may collect the data prior to implementation. • Align the RMPs for devices and drugs to a single review pathway. • Issue specific recommendations on how Health Canada will apply its new guidance in both the Clinical Trial Application (CTA) and market application.
3.2 Labelling requirements	• CPC encourages Health Canada to make combination product labelling requirements standalone and to not require combination products to meet both the drug and device requirements, which could potentially result in conflicting	• Align the use of electronic IFUs instead of only physical labelling. • Issue guidance regarding how to incorporate drug and device labelling

[6] 21 C.F.R. § 4.100−05 (2021).
[7] U.S. FOOD & DRUG ADMIN., POSTMARKETING SAFETY REPORTING FOR COMBINATION PRODUCTS GUIDANCE FOR INDUSTRY AND FDA STAFF (2019).

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	labeling requirements. CPC members have commented that while plain language labelling requirements are often difficult to apply to drug packaging, such requirements are even more difficult to apply to combination products, which may also require device labelling information. • CPC supports greater alignment with regards to use of electronic instructions for use (IFUs) instead of only physical labelling. Distribution methods for labeling for medical devices vs. drugs differ in Canada where medical devices used by professional users can be distributed electronically per Health Canada guidance.[8] Aligning labeling distribution pathways between devices and drugs/DDCPs would provide a consistent method by which professional users can find product information, IFUs, etc., and would allow for quicker distribution of critical information to users. However, while standardized formats for device IFUs would be helpful, the complexity in some of the device procedures may require more variation than would be acceptable in a Product Monograph. • CPC supports alignment with the EU MDR in how the MDR addresses quantitative and qualitative lists of "ingredients." Such alignment in these device requirements for Canada and the EU would also be helpful from a labeling perspective.	requirements for kits and multi-product packaging, such as those with multiple legal manufacturers. • Continue to follow PMOA as the basis for the labelling to avoid contradictions between labelling regulations for drugs and medical devices.
3.3 Quality assurance standards	• CPC agrees that gaps exist between the Good Manufacturing Practices (GMP) standards, CMP, and ISO requirements. CPC also believes gaps similarly exist with respect to Quality Agreements, release requirements, and temperature control (i.e., validation). • CPC encourages Health Canada to consider aligning to a hybrid GMP approach for DDCP, similar to FDA's current approach.[9] For example, a DDCP that has a drug as its primary component must comply with both the drug GMPs and the core elements from ISO 13485/QMS, including management responsibility, design, and development, purchasing, and monitoring and measurement. As with FDA's implantation, CPC requests that a "hybrid" approach based on drug GMPs would follow those inspectional and certification requirements instead of those for a device manufacturer. This is of particular importance in Canada, which requires use of the MDSAP process for certain classes of medical devices[10]; a streamlined approach for "integrated" and "co-packaged" combination products would allow for sponsors to more readily bring innovative products to market to address unmet medical needs. • CPC highlights that audits of foreign Medical Device Establishment Licence holders for importers are inconsistent.	• Consider aligning additional systems, such as Quality Agreements, release requirements, and temperature control. • Consider aligning to a hybrid GMP approach for DDCP, which could alleviate the need to use the Medical Device Single Audit Program (MDSAP) products when following a "hybrid" approach based on the drug GMPs. • Clarify how and when to audit foreign importers that are importing DDCP.

[8] HEALTH CANADA, GUIDANCE FOR THE LABELLING OF MEDICAL DEVICES, NOT INCLUDING IN VITRO DIAGNOSTIC DEVICES, § 21(2) (2015) (Can.).
[9] 21 C.F.R. § 4.1−4.4 (2021).
[10] *Medical Device Single Audit Program (MDSAP)*, GOV. OF CAN. (June 26, 2020), https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/activities/international/transition-medical-device-single-audit-program.html.

In addition, CPC suggests Health Canada consider the following:

1. Include pre-authorization (or premarket authorization) issues in the updated policy. Clinical Trial Application and Investigational Testing Authorization (ITA) are currently not synchronized and may use metrics that do not align.
2. Clarify the basis of including natural health products in the policy, particularly due to differences in the products' category, evidence base, and benefit/safety ratios.
3. Adopt clear definitions regarding the submission of foreign events or experiences and on reporting forms (E2B or email, fax, etc.) in its guidance documents. CPC encourages Health Canada to consider a streamlined approach to post-authorization safety reporting, similar to FDA's approach[11] to facilitate information sharing via how the product is registered (based on its PMOA). The CPC would appreciate separate guidance from Health Canada addressing this issue.
4. Consider including information on how sponsors could seek scientific advice for combination products in the updated Policy.

CPC appreciates the opportunity to provide input regarding Health Canada's DDCPs Issue Identification Paper. CPC hopes our comments are helpful and can inform Health Canada's analysis of the key considerations for updating its approach to classifying and regulating drug-device combination products. If the CPC can help further in any way, please do not hesitate to contact us.

Yours sincerely,

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On behalf of the Combination Products Coalition
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[11] 21 C.F.R. § 4.100 *et. seq.*