Proposed Regulation/Guidance Document:

Health Canada: Issue Identification Paper: Drug-Device Combination Products (DDCPs) Draft for Consultation

draft dated 2021/05/10

Comments from: International Society for Pharmaceutical Engineering (ISPE)

GENERAL COMMENTS ON THE DOCUMENT
In Section 1. Classifying drug-device combination products, the Policy should provide a clearly defined interpretation of the definition of a "combination product" and if needed, the Policy should clearly describe a streamlined mechanism for making this determination or adjudicating a product's combination product classification with the regulatory authority. For reference a good example for providing regulatory feedback on combination products, from an applicant's perspective is US FDA Guidance "Requesting FDA Feedback on Combination Products." https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requesting-fda-feedback-combination-products
Streamlining Regulatory Pathways for Combination Products: The Policy should be updated to have greater alignment between having a "single regulatory pathway" and appropriate "standards of evidence for product authorization" for combination products. As stated in the consultation document, the current Policy does not clearly define the appropriate regulatory pathway when a drug-enhanced device involves a device component of a higher risk class and the technical requirements are unclear if a drug-enhanced device is comprised of a Class II device as the primary component. It would be very helpful to applicants please if the updated Policy seeks to harmonize with the US FDA regulatory frameworks and best practices for combination products (See 21 CFR 3.2(e)). Under FDA's regulatory framework, a combination product is assigned to an Agency Center that will have primary jurisdiction (i.e., "the lead") for that combination product's premarket review and regulation. Assignment of a combination product to a lead Center is based on a determination of which constituent part provides the primary mode of action (PMOA) of the combination product. Regardless of the PMOA, the Agency Center with primary jurisdiction works with other Agency Centers to ensure adequate premarket review. This type of early interaction is very helpful to applicants.

Clinical Investigations: The consultation document does not discuss clarifying the appropriate pathways for filing a Clinical Trial Application (CTA) or Investigational Testing Authorization (ITA) for combination products. The updated Policy should seek to streamline the regulatory pathways for conducting combination product clinical investigations and should be in alignment with the Policy for obtaining a combination product marketing authorization.
Section 3.4 should include general principles for product lifecycle management for combination products based on principles developed in ICH Q12 "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management."
Further clarity is requested with definitions and possibly examples to differentiate kits vs. co-packaged products.
Further clarification is requested please regarding cross labelling where there is only a one-way label of a biologic or drug to a device (e.g., when the product information of the medicinal product refers to a specific device to be used and the device is obtained separately, or alternatively, when the product information of the medical device refers to a specific medicinal product to be used and the medicinal product is obtained separately).
In the next version of the revision of the guidance for DDCPs it would be helpful please if the section on post-authorization safety report contained more detail on expectations of what to report for both device and medicinal substance/product i.e. fields.
It would be helpful to describe in more detail those medical devices whose classification relative to DDCPs is unclear, for example hanging vials i.e. separate vials that are hanging and connected to the apparatus, that are activated and mixed and then administered through an IV set. It is suggested a phrase such as complex or uncharacterized medical device could be considered.
For improved usability/readability of the document it would be preferred to have the footnote entry on the respective page and not to have a full list of footnotes at the end of the document.
There seems to be a "page break issue" on pages 12/13 – please check.

Specific Comments on the Text

ISPE indicates text proposed for deletion with ~~strikethrough~~ and text proposed for addition with **bold and underlining**.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Page 3	DDCPs are health products that combine drugs and medical devices as a single entity	Create unique definition section	We suggest Including new terms and DDCP categories in a definition section for greater clarity
Page 3	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.	Suggest using definition as currently existing in Food and Drugs Act or adapt the definition on the Food and Drugs Act	The definition does not match the definition listed on page 12 (Appendix 1) and there is also no rationale provided why a different definition should be applied for Drug/Medical Device Combination Products. This is highly confusing for the reader and also not understandable why there should be different kind of drug definitions. Using the US definition would be an obvious benefit to applicants. Whatever definition is used, it would be helpful to applicants if recognition was made of definition used by other agencies.
Page 4	The Policy defines a “combination product” as: “a therapeutic product that combines a drug component and a device component (which by themselves would	We believe the combination product definition and policy should be interpreted in such a way as to consider single-integral, co-packaged, and cross-	Clarity on definition of “combination product” is required. In addition, to reduce regulatory burden on industry, we

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	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."	labeled combination products to be DDCPs	respectfully suggest that definitions be aligned with US FDA or EU MDR
Page 4	Co-packaged	The Policy requires greater clarification, product examples, and public jurisdictional decisions, as to why some co-packaged drugs and devices meet the definition of a "combination product", whereas others do not and require separate authorization for the drug and device components.	Adding product examples will illustrate the classification rule with much clarity. Therefore, suggested to include "...and product examples as to..." Also suggest publishing jurisdictional decisions regarding what has previously been regulated as a combination product in Canada. Currently, these prior examples are only available in summary basis of approval documents, so a sponsor would have to know in advance how the combination product had been classified, then search for the product in the drug or device summary basis of approval documents.

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Page 5	Drug delivery systems combined at time of manufacture…Examples include pre-filled syringes, transdermal drug patches, and drug-eluting disks	Examples include prefilled syringes **and** transdermal drug patches	A drug-eluting disk (assume spinal disk) appears to be a drug-enhanced device based on the information provided.
Page 5/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.	A kit consists of two or more health products that are contained in one package for convenience purposes but are not required to be **physically** combined prior to administration or use.	Add "physically" to provide clarity on the type of combination. Also recommended to give examples – e.g. a first aid kit.
Page 5	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.	Also included in the definition are products that are cross-labeled and combined prior to administration of the drug (e.g., when the product information of the medicinal product refers to a specific device to be used and the device is obtained separately, or alternatively, when the product information of the medical device refers to a specific medicinal product to be used and the medicinal product is obtained separately).	We agree with the paper's attempt to explicitly differentiate DDCPs from the broader combination product definition. We also agree with the definitions of drug delivery systems, which helpfully clarifies that an integral DDCP (combined at time of manufacture) and a co-packaged DDCP (co-packaged and combined prior to drug administration) are combination products that should be reviewed via a single regulatory pathway.

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			However, we suggest including cross-labeled drug delivery systems within the definition of DDCPs.
Page 5 co-packaged and combined prior to administration of drug	Co-packaged drug delivery systems classified by Health Canada as DDCPs include metered dose inhalers, as well as internal creams and their applicators.	Co-packaged drug delivery systems classified by Health Canada as DDCPs include **refillable and re-usable** metered dose inhalers, as well as internal creams and their **co-packaged** applicators.	A metered dose inhaler may also be combined at the time of manufacture – this should be clarified (or another example chosen, e.g. vial filled with drug and co-packaged syringe).
Page 5 Drug enhanced devices	In a device-enhanced drug, the drug component is the primary component.	In a device-enhanced drug, the drug component is the primary component. and the device must perform a function necessary to achieve the intended use of the drug product (e.g. controls the device, calculates dose, interacts with the device to record dose). Optional patient support tools for use with the drug (e.g. an adherence mobile app) are currently not considered devices or accessories, and thus should not be considered part of a combination product that is a device-enhanced drug.	The definition of device enhanced drugs in this paper does not make clear when a product would fall into this category and when it would not. Thus, we agree that an updated policy would need to address examples of drugs and devices that could be used in combination but are not considered DDCPs. This is important as the field of digital health is expanding, to differentiate an example such as the solid oral drug with an ingestible sensor from a drug that has an optional mobile app or tool to encourage adherence. The latter should not necessarily be considered combination products.

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Page 6 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.	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~~ typically ~~a~~ integrated in some way ~~singular entity~~ or combined prior to use (e.g. insertion of drug cartridge into device before injection) like co-packaged combination products, the Policy does ~~not~~ apply.	Cross-labeled products are not considered combination products because they are not integrated in a singular product. However, if these are both labeled for use together because both are necessary to achieve the intended use, then the two constituent parts are typically integrated together in some way prior to use (similar to a co-packaged combination product). As such, we suggest including these in the definition of drug delivery systems above, or at least specifying when some cross-labeled combination products would be considered drug delivery systems that should be reviewed through a single regulatory pathway.
Page 9 Labelling requirements	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	Principles as to what should be contained or included in an IFU for a DDCP could be provided as part of a revised policy or revised combination product regulatory guidance. Additionally, we request guidance regarding the potential review of platform IFUs to ensure efficient review of information that is the same across products.	The paper notes that there is no standardized format to be followed for a combination product IFU. In our experience, there is a specific format for the IFU steps for drug-led combination products, and it is clear how these should be incorporated into the Product Monograph. As such, we interpret this section as only applying to standalone

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	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…		devices or device-led combination products. Each DDCP will have its own steps involved in the administration. Additionally, the format of the IFU is often tested vigorously by sponsors for usability, to ensure patients can use it to safely and effectively administer the drug. As such, while principles as to what Health Canada's expectations are could be helpful and promote consistency across products, we suggest that sponsors not be constrained to use a specific format or template that some patient populations may find difficult to follow. Where an IFU is utilized across products that incorporate the same device, the content in this platform IFU that is duplicated across products should be considered in a single review, rather than re-evaluated each time the device is used in a new product. This enhances regulatory efficiency and avoids having different content in the IFU across products. Of course, new information in the IFU that is

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			related to the specific drug-device combination would be reviewed as appropriate with the labeling for the new combination product.
Page 9/ Quality assurance standards	…However there are differences in the respective standards for drugs and devices which affect the regulation of DDCPs	Suggest maintaining current approach.	We agree that duplication exists in the drug and device quality management systems. Given the duplication in the drug GMP requirements and the ISO device requirements, we agree with the current policy for a DDCP, which 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. We believe this is the appropriate approach and should be maintained to allow flexibility.
Page 10	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	Specifically, packaging requirements under GMP apply only to the direct packaging of a drug <u>at time of manufacture</u> and do not as a rule extend to the co-packaged device components <u>combined with a drug prior to administration</u> ~~that deliver a drug~~.	Suggested to have symmetry of description for single entity versus co-packaged products by adding "...at time of manufacture." and "...combined prior to administration."

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	drug delivery systems that are combined prior to administration.	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	