Combination Products Coalition

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VIA ELECTRONIC SUBMISSION

Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Docket No. FDA-2013-D-0350; Select Updates for Biocompatibility of Certain Devices in Contact with Intact Skin: Draft Guidance for Industry and FDA Staff

To Whom It May Concern:

The Combination Products Coalition ("CPC")[1] welcomes the opportunity to provide comments on FDA's "Select Updates for Biocompatibility of Certain Devices in Contact with Intact Skin: Draft Guidance for Industry and FDA Staff" dated October 15, 2020 (the "Draft Guidance").

The CPC generally agrees with the concepts proposed in the Draft Guidance, and appreciates FDA's recognition of the low risk posed by various common device materials that contact intact skin. Our comments, which are provided in the following table, focus on areas of the document that we believe would benefit from additional clarity. We also recommend inclusion of combination products within the scope of the Draft Guidance.

We appreciate the opportunity to provide input on the Draft Guidance, and ask that the Agency consider this feedback as it finalizes the Draft Guidance. In addition, we welcome the opportunity for further dialogue with the Agency to clarify or discuss any of our suggestions.

Very truly yours,

Bradley Merrill Thompson
On behalf of the Combination Products Coalition

[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 FDA 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.

Section #, Line #	Text in Guidance	Proposed Comment and Recommended Edit(s)	Rationale for Change
I. 17-19	The existing guidance "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process,'" (2016 Biocompatibility Guidance)	The existing guidance "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process,'" (2020 Biocompatibility Guidance)	The 2016 version is cited throughout the Draft Guidance, but the most current version of the FDA Guidance of ISO 10993-1 was released in 2020.
II. 38-44	…preparing premarket approval applications (PMAs), humanitarian device exemption (HDE) applications, investigational device exemption (IDE) applications, premarket notification (510(k)) submissions, and De Novo classification requests (De Novo requests) for medical devices that come into direct contact or indirect contact with the human body…	Add IND, NDA and BLA to this list: …preparing premarket approval applications (PMAs), humanitarian device exemption (HDE) applications, investigational device exemption (IDE) applications, investigational new drug (IND) applications, new drug applications (NDA), biologics license applications (BLA), premarket notification (510(k)) submissions, and De Novo classification requests (De Novo requests) for medical devices that come into direct contact or indirect contact with the human body…	This guidance should not only apply to products under CDRH, but also to CDER- or CBER-based submissions for the same nature of contact. Therefore, components of combination products that are in contact with intact skin should also be in scope of this Draft Guidance as they pose the same level of risk as other medical devices that are in scope.
III.(A)(1) 99-100	(1) Which Types of Devices are Included?" Devices included in this policy should meet all of the following characteristics:	(1) Which Types of Devices and Combination Products are Included?" Devices and device constituents of combination products included in this policy should meet all of the following characteristics:	We suggest FDA consider including within the scope of the document combination products having all characteristics outlined in Section III.A (1) *Which Types of Devices are Included*, as a skin-contacting material on an inhaler is no more likely to trigger an unacceptable adverse biological response resulting from contact of the material with the skin than that same material used in a medical device covered by this Draft Guidance, assuming proper compatibility between the drug and the device materials is evaluated.
III.(A)(1) 102 - 105	"Medical devices that contact intact skin surfaces only," as described in section 5.2.2 (a) of International Standards Organization (ISO) 10993-1:2018: Biological evaluation of medical	We suggest that application of the Draft Guidance not be limited to medical devices that contact intact skin, and be expanded to include	Some devices have skin contact surfaces and also surfaces or components that may have another contact type (e.g., tissue contact for

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	devices – Part 1: Evaluation and testing within a risk management process,	the skin contact materials for devices which may have other contact types.	adhesives or indirect contact with blood for drug delivery fluid paths.)
III.(A)(1) 110-122	FDA recommends additional discussion through the Q-Submission process to determine if this policy could be applicable to specific products in the following situations: If it is a combination product or biologically-derived material. Such products can cause adverse biological responses (e.g., cytotoxicity, irritation, or sensitization).	We suggest including similar language as noted below from the FDA Guidance for Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process," which states: 'Note that if your product is a combination product with a device constituent part, the general principles of this guidance would apply.'	We suggest inclusion of similar language for combination products in the Draft Guidance to note that the same general principles apply to applicable combination products that 1) contact intact skin surfaces only and 2) are composed of materials listed in the Draft Guidance. Currently, the Draft Guidance only mentions device submissions. It is acknowledged that on-body injectors attached via adhesive are specifically excluded from this guidance (line 161); however, there is no mention of applicability to drug/biologic PMOA combination products. It is also acknowledged that devices that contact breached or compromised skin are excluded (line 161), but pen and autoinjector products, for example, do not contact breached or compromised skin, so clarity regarding applicability of the document for these types of devices would be helpful. Furthermore, if this Draft Guidance is applicable to certain combination products, FDA should clarify whether there are differing expectations for clinical submissions (IND) vs. marketing applications or postmarket changes (NDA, BLA).
III. 124-126	(2) What Materials are Included? FDA has identified specific device materials that are included in this policy when they are in contact with only intact skin surfaces. The included device materials are:	Add the following materials to the "What Materials Are Included" list: Glass/ Borosilicate Glass Polystyrene Paper/Cardboard	Glass, paper and SS are used in household food wares and have a long history of safe human skin contact. Titanium is exempt from biocompatibility testing for some bone replacement implantable devices.

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		SS (surgical grade) & Titanium	
III.(A)(2) 131 and 161	Line 131, III.A(2) –Cured epoxy adhesives are included as low risk material. Line 161 Table 1, III.A(3). Adhesives used to attach a device directly to skin are excluded because they can cause irritation.	Please provide details on the assessment of adhesives which lead to low/moderate/high risk outcome. Please provide considerations which may include, but are not limited to, the types of adhesives, the curing process and the condition of skin contact surface (intact, breached, compromised).	Lines 131 and 161 appear to contradict each other with respect to the risk of adhesives. We ask that FDA clarify this apparent discrepancy.
III.(A)(5) 210-215	When the device is intended for use in a patient population that may not have the ability to identify adverse biological reactions related to cytotoxicity, irritation, or sensitization (e.g., patients with epilepsy or dementia), FDA recommends that manufacturers using this policy, in lieu of conducting biocompatibility testing, inform caretakers in the labeling by including a precaution discussing common adverse skin reactions.	When the device is intended for use in a patient population that may not have the ability to identify adverse biological reactions related to cytotoxicity, irritation, or sensitization (e.g., patients with epilepsy or dementia or the vision impaired), FDA recommends that manufacturers using this policy, in lieu of conducting biocompatibility testing, inform caretakers in the labeling by including a precaution discussing common adverse skin reactions.	In this statement, a suggestion for the Agency's consideration is to include the vision impaired patient population. They often cannot see or realize that a rash/light skin reaction is forming due to the medical device until it becomes more serious.