Contains Nonbinding Recommendations

Draft – Not for Implementation

Select Updates for Biocompatibility of Certain Devices in Contact with Intact Skin

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on October 15, 2020.

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document, contact the Office of Product Quality and Evaluation (OPEQ)/Clinical and Scientific Policy Staff at CDRH.Biocomp@fda.hhs.gov or (301)-796-5701.

When final, this guidance will update Sections II and III and add a new Attachment to "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process,'" issued on June 16, 2016.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Preface

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please include the document number 19007 and complete title of the guidance in the request.

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Select Updates for Biocompatibility of Certain Devices in Contact with Intact Skin

Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

FDA developed this draft guidance to propose select updates to FDA's current thinking regarding the type of biocompatibility information that should be provided in a premarket submission for certain devices made from common polymers and fabrics that are in contact with intact skin. 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,'"[1] (2016 Biocompatibility Guidance) remains in effect, in its current form, until this draft guidance is finalized. The proposed sections referenced below are intended to add or supersede applicable sections of the 2016 Biocompatibility Guidance after FDA considers public comment to this draft guidance. The sections of the 2016 Biocompatibility Guidance that are not affected by this select update will not be substantively changed and will remain in effect.

For the current edition of the FDA-recognized consensus standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database.[2] For more information regarding use of consensus standards in regulatory submissions, refer to the FDA guidance titled "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices."[3]

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-international-standard-iso-10993-1-biological-evaluation-medical-devices-part-1-evaluation-and.
[2] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm.
[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/appropriate-use-voluntary-consensus-standards-premarket-submissions-medical-devices.

FDA's guidance documents, including this draft guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Background

We are issuing this guidance to propose select updates to our biocompatibility recommendations and to assist manufacturers in 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[4] to determine the potential for an unacceptable adverse biological response resulting from contact of the materials of the device with the body.

III. Select Updates

A. New Attachment to the 2016 Biocompatibility Guidance: Biocompatibility of Certain Devices in Contact with Intact Skin

Many devices have intact skin contacting materials that are made from polymers and fabrics. FDA believes that these materials pose a very low biocompatibility risk because they have a long history of safe use in medical devices that contact intact skin. For such devices, significant FDA review resources are expended to obtain sufficient rationales to justify omission of biocompatibility testing for frequently used intact skin contacting medical devices, consistent with FDA's recommendations in the 2016 Biocompatibility Guidance.

This Attachment describes a least burdensome[5] approach for these devices that recommends specific material information to be included in a premarket submission in lieu of biocompatibility testing. This approach also supports the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible.[6] This approach is partially based on FDA's review experience in premarket submissions with these common polymers and fabrics.

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[4] For the purposes of this document, the term "human body" refers to either patient tissues or the clinical practitioner. For example, we recommend that you assess masks or gloves intended for protective purposes by clinical practitioners for biocompatibility. Similarly, we recommend that you also assess medical devices, such as implants or skin electrodes, for biocompatibility.

[5] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/least-burdensome-provisions-concept-and-principles.

[6] Russell WMS, Burch RL. The Principles of Humane Experimental Technique. London: Methuen & Co.; 1959. Special edition published by Universities Federation for Animal Welfare, 1992. Available online at: http://altweb.jhsph.edu/pubs/books/humane_exp/het-toc.

This approach also relies on certain parts of the Quality System Regulation (QS Regulation, 21 CFR 820) and other postmarket controls[7] to identify potential biocompatibility-related issues.

For example, quality system and other postmarket controls have requirements that should identify biocompatibility issues for devices in contact with intact skin if procedures established and maintained, and records maintained in the Device Master Record[8], by the manufacturer include sufficient:

- Purchasing controls (21 CFR 820.50) over material suppliers,
- Production and process controls for manufacturing (21 CFR 820.70). Manufacturing materials that could adversely affect device biocompatibility should be removed or limited to an amount that does not pose toxicity concerns,
- Receiving, in-process, and finished device acceptance (21 CFR 820.80) for component and manufacturing materials,
- Analysis of quality data (21 CFR 820.100(a)(1)), including complaints, to detect quality problems, such as those that may reveal issues of cytotoxicity, irritation, or sensitization. FDA recommends that such an analysis occurs routinely (at least annually), and
- Complaints (21 CFR 820.198) should be received, reviewed, evaluated, and, when necessary, investigated.[9] We recommend that manufacturers process complaints in a uniform and timely manner to look for issues related to cytotoxicity, irritation, or sensitization. Indications of these issues may include:
    - redness (erythema),
    - swelling (edema),
    - irritation,
    - sensitization (delayed Type IV hypersensitivity),
    - allergy, and
    - immune response or other reactions on the skin where the device has contact.

After FDA finalizes this guidance, FDA intends to periodically reassess the list of device materials and exclusion characteristics identified in Sections III.A.(2) and III.A.(3) below of this guidance. FDA recommends that external stakeholders submit comments to the docket to suggest the addition or removal of device materials or exclusion characteristics from this policy, including a rationale. FDA intends to review comments received in the docket and periodically assess whether any changes to this policy are warranted. When FDA believes changes are warranted, FDA will issue updated guidance in accordance with the procedures in the Good Guidance Practices Regulation (21 CFR 10.115).

(1) Which Types of Devices are Included?

Devices included in this policy should meet **all** of the following characteristics:

[7] For example, see 21 CFR 803.
[8] 21 CFR 820.181.
[9] Pursuant to 21 CFR 820.198(a)(3) and 820.198(d), complaints can represent events that must be reported to FDA under 21 CFR 803.

- "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 devices – Part 1: Evaluation and testing within a risk management process*,
- Limited (≤24 hour), prolonged (>24 hours to 30 days), and long-term (>30 days) durations of contact, including repeat use devices, and
- Composed of materials outlined in Section III.A(2) below.

FDA recommends additional discussion through the Q-Submission process[10] to determine if this policy could be applicable to specific products in the following situations:

- If a legally US-marketed device made from the same material was found to be toxic in previous testing;
- If a legally US-marketed device made from the same material resulted in adverse clinical findings after marketing that may be related to cytotoxicity, irritation, or sensitization;
- If the proposed device is indicated for use with neonates. Neonatal skin is more permeable, and therefore the risk that leachables may permeate the skin is higher;
- If the proposed device is indicated for use in pregnant women. If chemicals absorb through the skin, they may be transferred from a pregnant woman to her fetus; or
- If it is a combination product[11] or biologically-derived material. Such products can cause adverse biological responses (e.g., cytotoxicity, irritation, or sensitization).

(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:

Synthetic polymers:

- Acrylonitrile butadiene styrene (ABS);
- Cured epoxy adhesives;
- Fluoropolymers including polytetrafluoroethylene (PTFE), expanded polytetrafluoroethylene (ePTFE), polyvinylidene fluoride (PVDF), and fluorinated ethylene propylene (FEP);
- High impact polystyrene (HIPS);
- Polyamides, including nylon;
- Polybutylene terephthalate (PBT);
- Polycarbonate (PC);

[10] For more information, see FDA's guidance titled "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program." This guidance can be found at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

[11] A combination product is defined in 21 CFR 3.2(e).

- Polyetheretherketone (PEEK);
- Polyether imide (PEI);
- Polyethylenes, including low-density polyethylene (LDPE) and high-density polyethylene (HDPE);
- Polyethylene terephthalate (PET);
- Polymethylmethacrylate (PMMA);
- Polyoxymethylene (POM);
- Polyphenolsulfone (PPSU);
- Polypropylene (PP);
- Polyurethane (PU); or
- Silicone

Fabrics:

- Polyurethane fabrics, including Lycra;
- Cotton fabrics;
- Polyamide fabrics, including nylon; or
- Silk fabrics

(3) What Devices or Materials are Excluded?

Medical devices excluded from this policy are described in Table 1 below.

Table 1: Exclusion Characteristics

Medical Device Characteristic	Reason for exclusion
Intact skin contacting components fabricated from materials that are not explicitly included in the above list, including novel materials12 and bulk metals (e.g., titanium, stainless steel, nitinol, gold)	There are known risks or we do not have adequate experience with these materials that may introduce toxicity risks. Biocompatibility testing or detailed rationales for omission of this testing could address these concerns.
Stored in or containing fluids or creams	There is an increased risk that leachables can be transferred into the fluid or cream and then absorbed through the skin.
Fabricated from in-situ polymerizing materials, absorbable materials, or hydrogels	There is an increased risk that polymerization or degradation products can change over time. The manufacturing process can impact the type and quantity of intermediate and final chemicals present in the device, which could introduce a toxicity risk.
Contacts breached or compromised surfaces, such as abraded or shaved skin, or open or healing wounds	There is an increased risk that leachables can be transferred through breached or compromised skin.

[12] A novel material is a "material that has not been used in any legally US-marketed medical device," consistent with the 2016 Biocompatibility Guidance.

Reprocessed single-use devices	FDA is unaware of a history of safe use of single-use devices that are reused after reprocessing. Reprocessing of such devices can cause adverse biological responses (e.g., irritation)
Includes adhesives to attach a device directly to the skin (e.g., electrode pads, on-body pump attachment systems)	Adhesives can cause adverse biological responses (e.g., irritation)

(4) What Biocompatibility Information Should be Included in a Premarket Submission?

a. All premarket submissions (PMAs, HDE applications, IDE applications, 510(k)s, and De Novo requests)

We recommend the following information be included in the premarket submission for device types within the scope of the policy outlined in this guidance:

- A list of all materials used to fabricate the device with direct or indirect skin contact;
- A statement confirming (e.g., MDR analysis, literature search) that the listed materials have a documented history of safe use in legally US-marketed medical devices in contact with intact skin; and
- A statement confirming that none of the above listed exclusions apply.

b. Additional recommendation for IDE applications

In addition to the content recommended in Section III.A(4) above, FDA recommends that study sponsors discuss any adverse biological responses from devices within this intact skin policy in IDE progress reports[13] submitted pursuant to 21 CFR 812.150(b)(5). Specifically, FDA recommends that study sponsors describe any redness (erythema), swelling (edema), irritation, sensitization (delayed Type IV hypersensitivity), allergy, immune response, or other reactions observed by investigators during the course of a clinical study with observations attributed to a specific device, if relevant.

c. Additional recommendations for marketing submissions (510(k)s, PMAs, HDE applications, and De Novo requests)

In addition to the content recommended in Section III.A(4) above, FDA recommends manufacturers include a statement that the manufacturer has documented in their Device Master Record (DMR) how they have determined that biocompatibility risks for their device are addressed such that biocompatibility testing, and a detailed rationale regarding manufacturing is not necessary. The following statement is an example of the format and content to support such an approach:

[13] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/suggested-format-ide-progress-report.

"We have documented in the Device Master Record (DMR) that biocompatibility testing (i.e., cytotoxicity, irritation, and sensitization), and a detailed rationale regarding manufacturing (based on the type of materials and nature of contact) are not necessary, as biocompatibility risks are addressed through reliance on relevant quality system requirements and postmarket controls related to:

- Purchasing controls (21 CFR 820.50) of device materials,
- Production and process controls (21 CFR 820.70) for manufacturing materials ,
- Acceptance activities (21 CFR 820.80) for component and manufacturing materials,
- Corrective and preventative action (21 CFR 820.100),
- Complaint files (21 CFR 820.198), and
- Medical device reporting (MDR) (21 CFR 803)."

(5) What is FDA's Recommended Content and Format for Certain Labeling Information Related to This Policy?

This section contains FDA's format and content recommendations for certain labeling information, and to help illustrate, FDA has provided an example. 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.

An example of a precautionary statement that follows FDA's recommendations is below:

> ***"Caretakers should assess patients for adverse reactions on the skin where the device has contact, such as redness (erythema), swelling (edema), irritation, sensitization (delayed Type IV hypersensitivity), allergy, immune response, or other reactions."***

IV. Other Proposed Select Updates

In addition to the new Attachment described above, the following updates are being proposed to the 2016 Biocompatibility Guidance for consistency with this policy. FDA has **bolded** all proposed new text to make clear what text is being added to the existing language:

- Section II. Scope (pdf p.6/68) – FDA intends to add the following <u>new</u> bullet to provide a reference in the body of the guidance to the new information in the attachment described in section III.A above:

  - **"Attachment [G]: Biocompatibility of Certain Devices in Contact with Intact Skin, describes the recommended submission contents for devices in contact with intact skin that are fabricated from common polymers and fabrics."**

- Section III. Risk Management for Biocompatibility Evaluations; A. Risk Assessment of the Medical Device, paragraph 1 (pdf. p.9/68): To be consistent with this new policy, FDA intends to add a new footnote at the end of the following paragraph as described below:

  - "The risk assessment should evaluate the final finished device. The Agency makes a clearance or approval decision for a medical device as it is supplied in its final finished form. The Agency does not clear or approve individual materials that are used in the fabrication of medical devices. Therefore, the risk assessment should evaluate not only the materials used in the device, but also the processing of the materials, the manufacturing methods (including the sterilization process), and any residuals from manufacturing aids used during the process.**new footnote"**

  - New footnote: "**See Attachment G for special considerations for FDA's recommended biocompatibility evaluation for certain devices in contact with intact skin that are fabricated from common polymers and fabrics.**"

- FDA intends to redesignate Attachment G in the 2016 Biocompatibility Guidance to be Attachment H to accommodate the new Attachment proposed in this guidance.