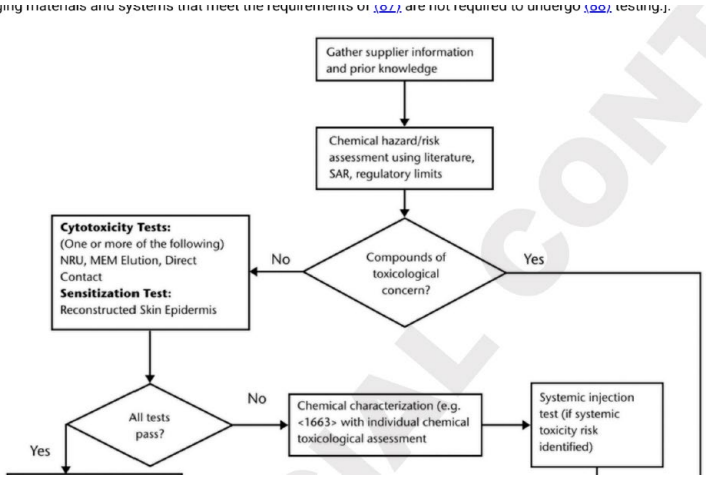
IPAC-RS Comments on Pharmacopoeial Forum 49(2) ***Chapter <1031> The Biocompatibility of Materials Used in Drug Containers, Medical Devices, and Implants***

General Comments

1. It should be clarified that the <1031> can be applied to the material constituents in a drug-device combination product, except for the secondary and tertiary packaging, if they are not in contact with the patient and/or the drug.
2. With respect to USP 1031, is it the case that there is no need to perform chemical characterization and toxicological assessment for elastomeric materials when USP 87 fails? Would one then directly perform USP 88?
3. Links between USP <1031> and USP <661.1> should be clarified. For example:

   USP<1031> provides a definition of a "Pharmaceutical Grade Plastic Packaging Material". A material that would pass cytotoxicy tests and irritation tests (2 of the 3 tests of USP <87>).

   USP <661.1> describes methods toward "well-characterized" "plastics of construction". Material must pass USP <87> genotoxicity?
4. Figure 1 notes the "Sensitization Test" (Reconstructed Skin Epidermis). This is not a sensitization test but the USP 87 "Irritation" test. Please clarify



5. This chapter often mentions "Sensitization Test", yet USP has noted that this test is to be removed – please clarify

6. <1031> End of section 3.1. The paragraph before the flow chart (Figure 1) discusses the term "Pharmaceutical Grade Plastic Packaging Materials" and replacement of Classification of Plastics Classes I-VI. The last sentence of this paragraph states NOTE – Elastomeric components for packaging materials and systems that meeting the requirements of <87> are not required to undergo <88> testing. Please explain the relevance of this statement as the new term is referring to Plastic Packaging Materials. Do the recommendations of this chapter also refer to elastomeric components and any other organic polymeric components used in primary packaging or delivery systems as mentioned in the previous paragraph? Should additional details clarifying the recommendations for these categories of materials be added to this chapter? Please see the comment about considering renaming Section 3.1 to include both materials.
7. <1031> We question how suppliers of materials (e.g., plastic resins) will be able to categorize their materials going forward – currently they use class I to VI, however the new pharmaceutical grade plastic packaging materials are assessed for the actual product/system (not just the material) – is the intention that the suppliers will just test to <87> and then only test <88> if required as per the Figure 1 flow chart, or to wait until the drug product manufacturer approaches them (as Section 3 paragraph 2 states 'The drug product manufacturer is responsible for gathering the information described above and managing the biocompatibility evaluation process. Because of the proprietary nature of specific component, material and process details, it may be necessary for a drug product manufacturer to establish a collaborative relationship with a unique component or material supplier to share information under conditions of confidentiality as is appropriate.'). Will the existing classification system be retained for existing materials? (Grandfathering rights for a defined period of time?)
8. <1031> section 6 states: Where legacy testing results are considered, the relevance of the methods to current practice should also be evaluated. To facilitate this evaluation, it would be beneficial if the USP could publish the legacy methods and/or change history document with the dates the methods were in place to enable this comparison to occur (the detailed methods may not be readily available to combination product owners when undertaking this review).

Specific Comments:

Page, Line or Section of the Document	**Original Language**	**Proposed Changed Language; or Comment**	**Justification of Proposed Change**
Section 2 (Scope) Line 5	[…]users should refer to additional device-specific FDA Guidance for Industries (1) . […]	[…]users should refer to additional device-specific FDA Guidance for Industries **(2) .** […]	Typo in references (reference (1) is the ISO 10993) *NOTE: valid also in other section of the document*

Page, Line or Section of the Document	Original Language	Proposed Changed Language; or Comment	Justification of Proposed Change
Section 3 (Overview of biocompatibility evaluation) Line 8	[…] including confirmation that the materials of construction meet food contact regulation […]	[…] including confirmation that the materials of construction meet food contact **and/or medical grade** regulation […]	Some materials are designed for medical industries and the supplier performs the grading evaluation against the medical regulations
Section 3 (Overview of biocompatibility evaluation) Line 20	Biocompatibility evaluation can include CSA of leachables and potential leachables (extractables) […]	Biocompatibility evaluation **could** include CSA of leachables **and/or** potential leachables (extractables) […]	Depending on drug form, the leachables could be not required
<1031> Section 3.1	Pharmaceutical Grade Plastic Packaging Materials	Pharmaceutical Grade Plastic/Polymeric Packaging Materials	The guidance mentions elastomeric materials in the introduction, then the focus moves primarily to plastic, as evidenced by the title of this section. Recommend that USP ensure elastomeric materials are mentioned/considered at the various stages through the document and perhaps use the term 'polymeric' when referring to both plastic and elastomeric materials. Modification of the title as indicated to reflect both options will meet this requirement and aligns with the nomenclature in the current version of the chapter.
Section 4	Compliance statement [e.g. USP	Compliance statement [e.g. USP	Some material are designed for

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(Risk based approach […]) Line 12	pharmaceutical grade plastic packaging material; food contact and safety ; […]	pharmaceutical grade plastic packaging material; **medical grade plastic packaging material**; food contact and safety ; […]	medical industries and the supplier perform the grading evaluation against the medical regulations
<1031> glossary	-	Pharmaceutical Grade Plastic Packaging Material	Define and add this to the glossary
<1031> glossary		Pharmaceutical Grade Polymeric Packaging Material	Define and add this to the glossary