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

General Comments

1. Overall the relationship between chemical characterization and biological reactivity testing remains unclear.
2. The scope of the chapter <1031> was extended by adding an overall biocompatibility evaluation process including chemical characterization. In the revised chapter 1031 requirements for packaging materials as the Chemical Suitability Assessment described in USP 661.2, 1661, 1663, 1664 are mixed with requirements for medical devices described in ISO 10993 part 18. The revised chapter 1031 does not clearly distinguish between those requirements. This leads on one hand to redundant information with respect to USP chapters 661.2, 1661, 1663, 1664 and ISO 10993, on the other hand it leads to confusion. Some of the evaluation steps are only required for medical devices, but not for container closure systems. Please enhance the evaluation of applicability, e.g., by denomination of decision criteria per step.
3. We would like to see <1031> be consistent with <88> in terms of the plastics designation system – specific comments provided.

Specific Comments:

Page, Line or Section	Original Language	Proposed Changed Language or Comment	Justification of Proposed Change
Briefing	1. Change the title to "The Biocompatibility of Pharmaceutical Packaging/Delivery Systems and Their Materials of Construction."	Change the title to "The Biocompatibility of Pharmaceutical Packaging/Delivery Systems and Combination Products including their Materials of Construction	Title needs to be aligned with Point 2, if the intent is to include both packaging and combination products materials.
	2. Expand the scope of the chapter to encompass plastic materials of construction and plastic and elastomeric components for pharmaceutical	2. Change in the scope of the chapter to encompass plastic materials of construction and plastic and elastomeric components for pharmaceutical	This clarifies that there has been a change rather than simple expansion.

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	packaging/delivery systems and for packaging of combination products.	packaging / delivery and combination products	
1. Introduction and Glossary	pharmaceutical packaging	Propose to define in more detail what is meant with pharmaceutical packaging, for example "definition pharmaceutical packaging = packaging material as part of the delivery system in contact with the drug product"	Differentiation between pharmaceutical packaging and delivery systems required. Packaging may be a main part of a delivery system (PFS) or not used at all in a delivery system (transdermal patch). The relevance of packaging of a delivery system in a biological evaluation can be very different, for example blister as packaging for an autoinjector compared to a peel pack for a transdermal patch. Propose to define in more detail what is meant by "pharmaceutical packaging."
2. Scope	…This chapter outlines a risk-based approach to biocompatibility evaluation that can be supplemented with the evaluation ….	This chapter outlines a risk based approach to biocompatibility, which includes the use of chemical characterization of materials of construction and/or packaging components/delivery systems and combination products	The intent to allow chemical characterization as an alternative to biological reactivity tests is clearly stated. What is less clear is how this is done. Can all biological tests be replaced with a chemical characterization? Can it be a mixture or purely biological tests?
2. Scope	…Information on a material of construction is necessary, but not sufficient, for a complete	Add language that makes clear what the gap is.	Does not make clear what "information" here means and therefore what is not adequate.

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	evaluation		
2. Scope	...direct contact with mucosal surfaces or other tissues during use	With this definition, contact with skin seems to be excluded. Please make clear, that packaging material or delivery systems that are in contact with skin are not to be considered. Alternatively categorization of ISO 10993 should be referred to.	Misleading
3 Overview of Biocompatibility Evaluation	Prior knowledge may contribute….can be used to further evaluate biocompatibility for a specific packaging/delivery system associated with a particular dosage form and route of administration	Add a table with list of requirements	Why not formalize the list of requirements in a table? This would aid clarity and understanding
3.1 Pharmaceutical Polymeric Material	Classifying material as Class I-VI in <88> was based ….	Suggestion to include in introduction rather than a separate section	This implies Pharmaceutical Grade Polymeric Materials are defined by USP <88>. Consider a revision of the title and better still consider removal of Section header and placement into the Introduction
3.1 Pharmaceutical Polymeric Material	Over time, a Class VI designation has become the predominant standard for evaluating and describing	Over time, ~~a~~ Classes V and VI designation ~~has~~ have become the predominant standard for evaluating and describing	For the inhalation industry, our requirements for plastic testing for inhaler components is Class V, not VI. It would be preferred that the text

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	polymeric materials including plastic materials of construction, plastic and elastomeric components, and any other organics polymeric components used in primary packaging or delivery systems for pharmaceuticals, leaving Classes I-V redundant. "Pharmaceutical grade polymeric materials" replaces Class VI in <88>. ……	polymeric materials including plastic materials of construction, plastic and elastomeric components, and any other organics polymeric components used in primary packaging or delivery systems for pharmaceuticals, therefore the distinction into six classes no longer serves a current purpose ~~leaving Classes I-V redundant~~. "Pharmaceutical grade polymeric materials" replaces any reference to the Classification previously used ~~Class VI~~ in <88>. …… OR Over time, ~~a~~ Classes V and VI designation ~~has~~ have become the predominant standard for evaluating and describing polymeric materials including plastic materials of construction, plastic and elastomeric components, and any other organics polymeric components used in primary packaging or delivery systems for pharmaceuticals, therefore the	either just says that the Class system is being replaced by one term, namely Pharmaceutical Grade or change the focus of the discussion to include Class V rather than VI. This should align with <88> as we have provided similar comments to that chapter.

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		distinction into six classes no longer serves a current purpose ~~leaving Classes I-V redundant~~. "Pharmaceutical grade polymeric materials" replaces any reference to Class V and Class VI in <88>. ……	
3.1 Pharmaceutical Polymeric Material		It is mentioned that this classification may applied to elastomers but in USP<381>, it is said that if USP<87> requirements are not met, USP<88> can be performed and when USP<87> requirements are met, there is no need to undergo USP<88> requirements – How will this approach be integrated? What about for elastomers used in orally inhaled and nasal drug products?	Clarification needed.
3.1 Pharmaceutical Polymeric Material	…It does not apply to inorganic materials, processing aids, additives or liquids	This last sentence is unclear, do inorganic materials, processing aids, additives, or liquids have a different requirement - if so what is it?	Clarification needed.

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3.2 Regulatory Expectations for Biocompatibility		This section does not include chemical characterization and thus is confusing as to its role in biocompatibility. Perhaps re-word as "Current regulatory expectations based on biological reactivity testing". This would then logically suggest a section is needed based on chemical characterization.	Clarification needed.
3.2 Regulatory Expectations for Biocompatibility	From a biological reactivity perspective, ….requirements in Table 1	Align Table 1 with this text. For example, Table 1 lists these test requirements for each route of administration together with the FDA Centers that regulate them; this includes listing in CFR and in-vitro and in-vivo tests. Table 1 includes also a requirement that is not an in-vivo or in-vitro test. This makes this sentence confusing. There should also be a fuller explanation of what compliance against the CFR means	Alignment would aid in understanding.
3.2 Regulatory Expectations for Biocompatibility	Three baseline tests …	Propose to use ISO 10993 endpoints: cytotoxicity, sensitization,	Harmonization of requirements

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		irritation	
3.2 Regulatory Expectations for Biocompatibility	Additional tests are required for packaging/delivery systems for combination products regulated as medical devices.	Change to: Depending on the nature of body contact and the duration of contact, additional tests may be required for the delivery system.	Depends on categorization according ISO 10993-1.
3.2 Regulatory expectations for Biocompatibility Table 1	Table 1 is not aligned with chapters 661.1, 661.2, and 381, where no tests according to chapter <88> are required or only if tests according to <87> failed.	Please align chapters.	Clarification needed.
	Table 1 does not fully reflect the expectations for medical device with regard to ISO 10993 and/or the FDA CDRH guidance, as some delivery systems may have also prolonged or long term contact.	Please revise the table accordingly.	
4. Risk based approach		Consider removing this chapter or clarifying relationship with other chapters, e.g., 661.1, 661.2, 381, and 1661, where risk based approaches are already described.	It is not clear how this section is linked to the packaging related chapters 661.1, 661.2, 381, and 1661, where risk based approaches are already described. The information here seems to be redundant. Information regarded

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			in this chapter exceeds the scope of the chapter, i.e. biocompatibility. Principles of risk evaluation for medical devices are transferred to packaging/drug delivery systems.
4. Risk-Based Approach to Biocompatibility Evaluation		As per comments above, suggest rewording the section header.	Linked to comment on last section -- is this supposed to be "Future Requirements for Biocompatibility testing"?
4. Risk-Based Approach to Biocompatibility Evaluation Figure 1	Gather Relevant Available Data		Add "Step 1" reference to diagram
	Conduct Risk Analysis	Suggest to reword as “Risk Identification”	Add Step 2 to diagram
	Gaps in acquired data?		Add Step 3
	Risk Evaluation Title of Figure 1. Biocompatibility Risk Evaluation Process	Re-word to Biocompatibility Risk Management	Risk Evaluation is surely the requirement to have acceptable bio-compatibility. The placement of risk evaluation and risk control is debatable. Should there be an evaluation after risk analysis to evaluate gaps and risk control / conduct testing to mitigate the risk?

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4. Risk-Based Approach to Biocompatibility Evaluation Step 1. Gather Information		Change text to read: "For the purpose of classifying the risk, ...should be identified"	Again, avoid word "evaluation" at this point in process. Suggestion is "For the purpose of classifying the risk, ...should be identified"
	"For components… following information should be obtained".	Revise to: "For components… following information to be obtained may include".	Since for all products depending on the degree of concern as per <1664> Table 1, not all information is required, the text should be revised. For example: "Leachables study results (internal use for pharmaceutical manufacturer)" have been listed as information that should be obtained. This is not consistent with step 3 where it is outlined that an extractable assessment can be conducted alternatively to understand potential leachables.
	Toxicological evaluation of test and/or test results	Suggest including the text in the leachable study and/or extractable study. Consider use of term, "Safety Risk Assessment" to replace Toxicological evaluation of test and/or study results - or define elsewhere for clarity	

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4. Risk based approach Step 3 Informal gap analysis and testing	In this section implants are mentioned, which are not part of Table 1 and not mentioned in the examples under scope.	Please make clear if implanted delivery systems are in scope and if so add the requirements described in ISO 10993 in Table 1, or make reference to them.	
	The listed biocompatibility tests in Table 1 seem to be incomplete, as in section 4 more tests are mentioned.	Align Table 1 and Figure 2.	
4. Risk based approach Figure 2 Biological reactivity test decision matrix	The decision tree does not reflect the established approaches of chemical characterization and toxicological evaluation of individual extractables / leachables using thresholds like safety concern threshold (SCT), qualification threshold (QT) or threshold of toxicological concern (TTC), as established, e.g., by the PQRI E&L recommendation.	Propose to follow the flowchart for chemical characterization process in ISO 10993 part 18, figure 1 and to follow table A.1 in ISO 10993 part 1 for selection of endpoints of biological evaluation.	Harmonization of requirements
Figure 2	Solid	Replace with “Solid Drug Product”	It is unclear what this means or requires

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	Chemical composition with toxicology assessment		
	Liquid	Liquid Drug Product	Consider placing Figure 2 placed before Fig 1 to establish what data might need to be collected.
	Chronic	This is unclear: Is the suggestion that both biological reactivity tests and chemical characterisation tests are required. What tests are required?	It is unclear what this means or requires
	Chemical Characterization	Again unclear on role of chemical characterisation in the process.	It is unclear what this means or requires
	Short Term	Suggest providing context and explanation regarding "chemical characterization as appropriate"	When is chemical characterization appropriate?
	Genotoxicity Concern	This is a requirement of the chemical characterisation - The suggestion is this would prompt a further biological reactivity test? (Same comment for Systemic toxicity concern and Other toxicity concern)	
5. Biological Reactivity Test considerations	The title of this section is called "biological reactivity test considerations".	Delete language regarding chemical assessments.	Considerations regarding chemical assessment should be part of USP 1663; or placed in the appropriate section of

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5.1 Test Article Selection and Sample Preparation			this chapter related to chemical assessments.
5.2 In Vitro Test Selection Table 2	Advantages; Neutral red uptake		Is the proposal that this is done in preference to others? Perhaps an order of preference would be useful to include; or a decision tree for selection of method.
5.2 In Vitro Test Selection Table 3			These are dose based tests - How can they be done on materials containing substances with at unknown concentrations
5.2 In Vitro Test Selection	The maximum test concentration will depend on cytotoxicity of the sample extract.	If cytotoxicity determination is an important prerequisite, then include in a decision tree.	
5.4 Development of Acceptance Criteria for In Vivo and In Vitro Tests Table 4	Cytotoxicity, Ophthalmic	Why is a lower reactivity grade suggested for Ophthalmic?	Clarification needed.

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7. Chemical Assessment	Assessment of biocompatibility or biological reactivity may be both complemented and supplemented by chemical characterization ….	No option of replacement? Is the chapter suggesting in-vitro testing will always be required?	Clarification needed.
7. Chemical assessment		Please make clear that the chemical assessment under section 7 is only necessary if a correlation between biological reactivity treat and chemical assessment is necessary, e.g., due to a failed biological reactivity test. Otherwise, extractables testing is performed following the approaches described in USP chapter 1663.	Clarification needed.
7.1 Chemical Assessment Correlation to Biological Reactivity Test Results		Are you suggesting chemical assessment as a rationale for failure of in-vivo and in-vitro ? This is unclear.	Clarification needed.