IPAC-RS Comments on Pharmacopoeial Forum *Chapter <88> Biological Reactivity Tests, In Vivo*

General Comments

1. The scope of this chapter beyond "Pharmaceutical Grade Polymeric Materials" is not defined and is unclear. Is it intended to apply in other areas?
2. Would this chapter, once finalized, be retroactive? What about for drug products already approved and marketed in US?
3. Will USP<661.1> & <661.2> will be updated and changed accordingly (before the application date planned in December 2025)?

Specific Comments:

Page, Line or Section of the Document	**Original Language**	**Proposed Changed Language**	**Justification of Proposed Change**
Page 1 Briefing	Delete *Classification of Plastics* because the distinction of plastic materials into six classes (Class I to Class VI) no longer serves a current purpose because in practice only Class VI is now utilized by vendors and end users	Delete *Classification of Plastics* because the distinction of plastic materials into six classes (Class I to Class VI) no longer serves a current purpose and is being replaced by one term, namely Pharmaceutical Grade *OR* Delete *Classification of Plastics* because the distinction of plastic materials into six classes (Class I to Class VI) no longer serves a current purpose because in	For the inhalation industry, our requirements for plastic testing for inhaler components is Class V, not VI. It would be preferred that the Briefing text 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 only VI

		practice only Class V and Class VI are now utilized by vendors and end users	
1.0 Scope,	Reference to USP chapters 661.1, 661.2 is made in the second paragraph	Clarify in which cases in vivo tests are required and align the chapters	Reference to USP chapters 661.1, 661.2 is made. In these chapters no biological reactivity tests in vivo are required, only in vitro tests as per USP 87 are required.
2.0 Pharmaceutical Grade Polymer Materials	…An implantation test is not required for polymeric….but may be required for …combination products..	List products requiring implantation	What combination device needs this? It must be a very small number and thus would be useful to define to avoid un-necessary use.
2.0 Pharmaceutical Grade Polymeric Materials	Pharmaceutical grade polymeric materials for packaging/delivery systems require application of the *4.0 Systemic Injection Test* and *5.0 Intracutaneous Reactivity Test* (Table 1). An implantation test is not required for polymeric materials used in packaging/delivery systems but may be required for packaging/delivery systems for combination products having a device component (see <1031>)	Pharmaceutical Grade Polymeric Materials for packaging/delivery systems require application of the *5.0 Intracutaneous Reactivity Test* and *7.0 Sensitization Test*. The *4.0 Systemic Injection Test* is not required for surface devices but is required in most cases for externally communicating and implant devices.	The requirement for the 4.0 Systemic Injection Test is inconsistent with what had previously been suggested in the <1031> *Table 3. Test Selection Matrix for Surface Devices*, where Systemic Injection Test was required. Please consider this suggested text.
3.0 Preparation of Extracts Table 2	Extraction Ratio	Consider adding justification for proposed ratios	Provides further understanding of the proposed recommendation

3.0 Preparation of Extracts Extraction Solvents	List of Solvents	Align solvent list with samples in Table 3	Six solvents listed. Only 5 in Table 3 (No WFI). Revision would add further clarity.
3.0 Preparation of Extracts Extraction Procedure		Please include a clear table of extraction times and temperatures, rather than buried in text.	
4.0 Systemic Injection Test Table 3	Test Material	Replace "Test Material" with "Test Extract"	Use of "material" in this context is confusing.
	Dose	Change to: "Max dose of test extract"	
4.0 Systemic Injection Test; Test Animals	The values listed are intended to be informative and represent….	Comment: If limits here are informative only then results will vary depending on dose administered. This seems to illustrate the subjective nature of these tests	
	Table 3 does not apply to natural elastomers…	Suggest adding a column to Table 3 to clarify use. Further, add elastomers to the column, rather than in a footnote.	Provides further clarification
	Inject each of the 5 mice…		Why have this as a footnote? Why not clearly describe in preparation?

4.0 Systemic Injection Test Acceptance Criteria		Consider making these acceptance criteria less subjective, e.g., list the factors that must remain unaffected for a pass and set a range.	Less subjectivity.
5.0 Intracutaneous Reactivity Test		It is unclear which extracts could be used for this test. Suggest creation of a separate "Table 3" for each test or an expanded Table 3 that clearly shows use.	Provides for clarity an improved understanding
5.0 Intracutaneous Reactivity Test Procedure	For each sample extract, use 3 animals….	Clarify if this includes any of the IP solutions? No clear indication of volume to inject. Also, same comment as above -- add this preparation step to extraction section for clarity. Suggest introducing an "Evaluation" section separate from procedure. Alternatively, move Acceptance Criteria header to here.	
5.0 Intracutaneous Reactivity Test Table 5		This needs to be moved forward to beginning of section (procedure)	
6.1 Intramuscular Implantation	"keep the animals for a period of not less than 120 h and…"	Consider the use of this test	It is suggested to keep animals for a period not less than 120h then evaluate encapsulation at the implant site. Is

in Rabbits; Procedure and Table 7			this long enough for any meaningful result? Is this test fit for purpose?