IPAC-RS
International Pharmaceutical Aerosol Consortium on Regulation & Science

1500 K Street NW • Washington DC • 20005
Telephone +1 202 230 5607 • Fax +1 202 842 8465
Email info@ipacrs.org • Web www.ipacrs.org

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Desmond G. Hunt
Principal Scientific Liaison
US Pharmacopeial Convention
12601 Twinbrook Parkway, Rockville, MD
20852-1790

Dear Dr. Hunt,

The following are comments submitted to the USP by the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) on the Pharmacopoieal Forum stimulus article *USP's Approach for Future Revision of Biological Reactivity Chapters ⟨87⟩, ⟨88⟩, and ⟨1031⟩.* IPAC-RS thanks USP for this opportunity to provide comments.

IPAC-RS agrees generally with the concepts proposed to revise these chapters. We welcome the proposal to revise the chapters within a science- and risk-based framework. A risk-based approach, taking into account the chemistry composition of the materials, existing literature and the end-use of the materials is more appropriate than a "blanket" set of testing. Further, implementing the "3Rs" is of paramount importance and the proposed structure balances patient safety versus animal testing, cost and inherent risk. Finally, we agree that the implantation test is not relevant and can be removed.

Alignment among ISO 10993-1 and USP Chapters

We welcome the suggestion that USP would integrate with ISO10993-1:2018 in this move towards USP<87> plus risk-based assessment. The suggested revised approach seems to align well to the risk-based approach of ISO10993-1:2018, and the utility of chemical characterization as a key part of the overall safety assessment process with evaluation and risk assessment rather than default testing.

We suggest that USP progress and assure alignment with ISO10993-1:2018 as the global environment and the European Union Medical Device Regulation will use ISO10993-1:2018, and it is helpful if there is alignment globally (where applicable). We also note that CDRH review devices alongside CDER for, e.g., drug device combination products, and they are used to using ISO10993-1:2018. We note that ISO10993-1:2018 is risk based but with no emphasis on in-vitro, so if USP provides for risk-based approaches, appropriate tests and chemical information, one could therefore go to ISO10993 and provide information to justify the evaluation, and provide complementarity.

As there is overlap between biocompatibility requirements for materials used in pharmaceutical applications and medical devices, wording in the USP Chapters should take into account that some delivery systems may also be classified and regulated as a medical device. This is the case for drug device combination products. In this case, the biocompatibility requirements may be different than those outlined in this stimulus article and in the current USP chapters. The ISO 10993 table included in the current chapters should align with that included in the ISO 10993-1:2018.

We suggest that any revised chapters clarify its focus, e.g., on material of construction, on components, both? Biocompatibility for final finished device components would follow ISO 10993 series of testing based upon the intended nature and duration of patient contact, and so again, alignment and complementarity with those standards is important. Biocompatibility of a medical device may (and often does) include assessments beyond those indicated in the stimulus article (chemical information, implantation (local toxicity) in addition to cytotoxicity) and what is needed depends upon the nature and duration of contact.

Class VI Testing and "Pharmaceutical Grade"

General experience reflects what is stated in the article, i.e., that the most stringent classification, Class VI, has been utilized as the default for all polymeric materials regardless of risk or material type (plastic, elastomer, etc.). Class VI testing has typically been conducted by default as a guarantee to regulatory approval, rather than a true reflection of risk.

We welcome a better understanding of 'pharmaceutical grade' (note that it would need to be aligned with ISO10993-1:2018, see above comments). It is important that 'pharmaceutical grade' is clearly defined; if it is not, then the most stringent set of tests will remain the default -- and since suppliers will test in hopes to supply the pharmaceutical industry, such change will not result in a testing reduction. Would plastics be defined as 'pharmaceutical grade' only when they pass a certain defined set of tests?

In addition, it is not clear what might constitute 'non-pharmaceutical grade,' in the context of a pharmacopoeia. If 'food grade' material is acceptable to use in medical devices, how would this then relate to 'pharmaceutical grade' materials? An ability to retain existing 'food grade' materials with additional justifications would be important and helpful. Phase appropriate use of 'food grade' would be desirable to enable early development and clinical use without significant delays, with subsequent progression to the appropriate grade for the long term product development/approval. Consideration of how 'food grade' may be used in the development process and for certain 'low risk' products, is also aligned with a risk-based approach. A more in-depth discussion of these two grades and how they are appropriate would be beneficial.

Please also note that 'pharmaceutical grade' should not just fulfill biocompatibility but also consistency of the formulation, security of supply, change management, etc, as noted in the existing VDI consensus standard on medical grade materials.[1]

[1] VDI 2017:2019-07, Medical Grade Plastics (MGP). July 2019. https://www.beuth.de/en/technical-rule/vdi-2017/307527917

In Vitro Testing

Additional guidance on actions in the event of "failure" of in vitro tests is also paramount. For example, what action would need to be taken if one of multiple tests fails?

We look forward to seeing further, more detailed proposals in the following areas, as it is somewhat difficult to comment currently due to their general descriptions in the stimulus article:

- The stimulus article mentions, "…in-vivo testing, which would be performed only when deemed necessary by risk assessment". How would such risk assessments be done; in particular, how might a supplier conduct these risk assessments?

- The current <87> includes three version of a basic cytotoxicity test (Agar diffusion, Direct Contact and Elution Test). Only one of these is an extract based test (Elution Test). The current proposal adds the Neutral Red Uptake test, but provides no information on how these tests could be implemented. There is the potential to have more sophisticated treatment of cytotoxicity with quantitative assessment of parameters such as membrane integrity. It would be beneficial to consider such treatments in discussions and considerations of using in-vitro measurement to replace in-vivo testing.

- Chapter 87 could be revised to allow additional in vitro tests that are validated (e.g., irritation).

- Implementation of genotoxicity tests on extracts and mixtures. These in-vitro tests are done typically on fixed concentrations of known identity. It is unclear the value of a test in cases where the mixture is unclassified. If this is to be paired with extractable analysis of mixture, the approach seems counter to the chemical safety approaches described in the proposed <1031> Table of Contents.

- Will the proposed revisions address unidentified compounds (extractables), as SAR would not be able to be performed without an identified structure?

Considerations for <1031>

More details regarding a "risk assessment approach" in <1031> would be helpful, including defining a process for utilizing chemical characterizations as part of the overall safety assessment process. The chemical assessment (extractable and leachable testing), will need a discussion of thresholds and a clear workflow. We would be interested in contributing to such conversations.