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Bioreactivity testing in single use technologies; industry position paper

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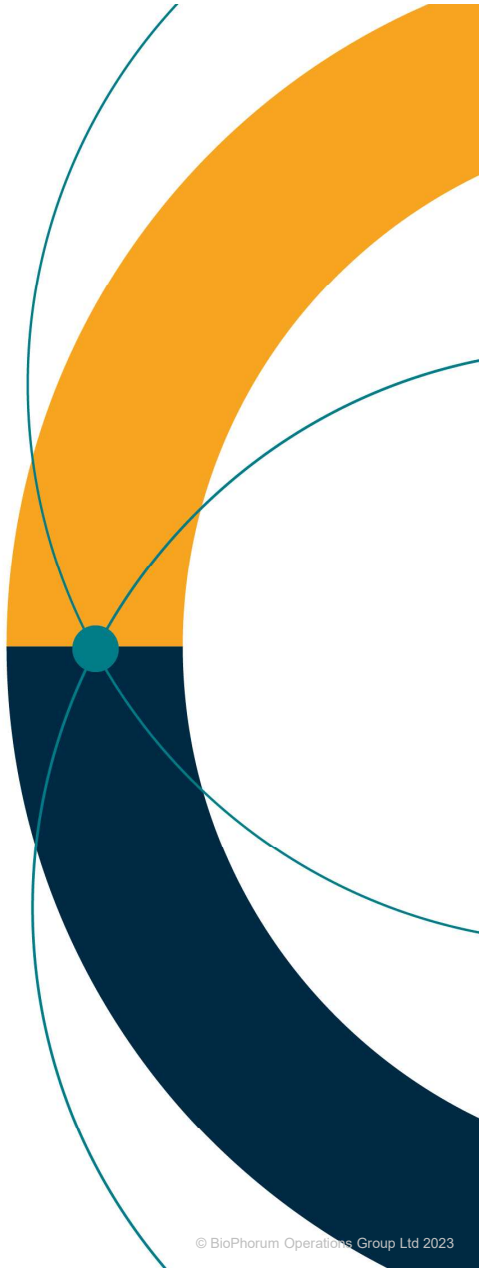
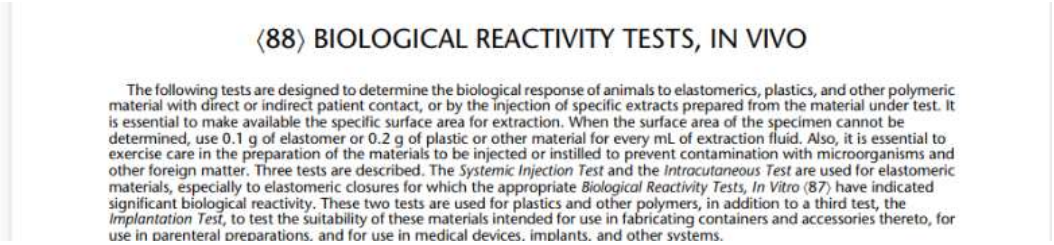


History of Bioreactivity Testing in Single Use Technologies

- Adoption of Single Use Technologies in biomanufacturing processes has increased significantly in the last 25 years
- It is crucial to demonstrate that these products are safe and suitable for their intended use
  - Historically, the primary test to establish safety of a material has been biocompatibility
- A long-standing challenge exists regarding the best methods to qualify and validate single use components
- Regulatory standards addressing single-use technologies used in biomanufacturing processes are also lacking, adding to the complexity
- Practices used for related products/industries have been adopted and adapted for SUT
  - E.g. drug products in contact with plastic packaging, container closure systems and the medical device industry
- Reliance on USP <88> (and others) was born out of these circumstances



⟨88⟩ BIOLOGICAL REACTIVITY TESTS, IN VIVO

The following tests are designed to determine the biological response of animals to elastomerics, plastics, and other polymeric material with direct or indirect patient contact, or by the injection of specific extracts prepared from the material under test. It is essential to make available the specific surface area for extraction. When the surface area of the specimen cannot be determined, use 0.1 g of elastomer or 0.2 g of plastic or other material for every mL of extraction fluid. Also, it is essential to exercise care in the preparation of the materials to be injected or instilled to prevent contamination with microorganisms and other foreign matter. Three tests are described. The *Systemic Injection Test* and the *Intracutaneous Test* are used for elastomeric materials, especially to elastomeric closures for which the appropriate *Biological Reactivity Tests, In Vitro* ⟨87⟩ have indicated significant biological reactivity. These two tests are used for plastics and other polymers, in addition to a third test, the *Implantation Test*, to test the suitability of these materials intended for use in fabricating containers and accessories thereto, for use in parenteral preparations, and for use in medical devices, implants, and other systems.

Current State

- SUT market is growing with more technologies/materials being introduced
- Important to define what testing is essential when introducing any new SUT to the market
- USP <88> / Class VI has become *perceived* to be a non-negotiable, dogmatic regulatory requirement by biopharmaceutical manufacturers and suppliers
- However, **no regulations exist** that stipulate *in vivo* testing as a requirement for single-use technologies
- Some testing labs are starting to decline requests for USP <88> testing unless evidence can be given that it's required by regulators
  - Documents requested are 510(k) submissions (US) or equivalent European directives which only apply to medical devices
- The purpose of this presentation and associated stimulus article is to revisit the assumed need for USP <88> / Class VI for SUT and work towards industry alignment on ensuring testing is proportionate to the assessed risk

Overview of Testing

- Standards for plastics used for pharmaceutics started to be developed by the U.S. Pharmacopeia and National Formulary (USP–NF) in the 1960s
- The chapter “Biological Tests— Plastics Containers” published in 1965 aimed to mitigate any potential impact on patient health due to plastics
- Plastics were assigned Classes I–VI based on biological in vivo testing
- That chapter later became USP <88> with Class VI being the most rigorously tested class
- Specific extraction solvents, temperatures and durations (see table)
  - Systemic Injection Test – extract injected either intravenously or intraperitoneally
  - Intracutaneous Test – extract in contact with live subdermal tissue
  - Implantation Test – material implanted intramuscularly or subcutaneously into the animal
- USP <88> failures are very rare so it is not serving as a true material qualification test
- The ISO standards 10993-6, 10 & 11 are aligned to USP <88> and as such are also within scope of this work

Test	Extraction Solvent	Extraction Conditions	Plastic Classes						Animal
			I	II	III	IV	V	VI	
Systemic Injection (IV)	Sodium Chloride	50 °C (122 °F) for 72 hours 70 °C (158 °F) for 24 hours 121 °C (250 °F) for 1 hour	x	x	x	x	x	x	Mouse
Intracutaneous			x	x	x	x	x	x	Rabbit
Systemic Injection (IV)	Alcohol			x	x	x	x	x	Mouse
Intracutaneous				x	x	x	x	x	Rabbit
Systemic Injection (IP)	PEG 400				x		x	x	Mouse
Intracutaneous							x	x	Rabbit
Systemic Injection (IP)	Vegetable Oil				x	x	x	x	Mouse
Intracutaneous						x	x	x	Rabbit
Implantation Test (IM)	Implant strips of sample	Not Applicable				x		x	Rabbit
Implantation Test (SC)	Implant sample					x		x	Rat

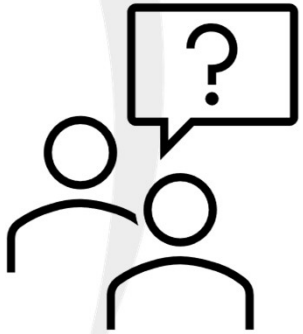
Table recreated from: United States Pharmacopeia (2023). *General Chapter, ⟨88⟩ Biological Reactivity Tests, In Vivo*. USP-NF. Rockville, MD: United States Pharmacopeia.

BioPhorum Survey on Bioreactivity Testing in Single Use Technologies

- In September of 2021, BioPhorum conducted a survey to assess the use of U.S. Pharmacopeia USP <87> Biological Reactivity Tests *in vitro*, and USP <88> Biological Reactivity Tests *in vivo*
- A total of 26 responses were received from single use system (SUS) manufacturers, regulatory and medical technician teams
- Of those responses, 83% said they would support a change in testing for single-use components from USP <88> to USP <87> (or ISO 10993-5), with 96% agreeing that an industry statement on the validity of this switch would be useful
- This change would remove the requirement to test on animals, moving to a more sustainable method of testing, and focusing more on applicability and higher quality tests
- A published industry consensus and alignment on how to navigate this change is needed to eliminate uncertainty
- There is already broad consensus that USP <88> can be discontinued, but firmly establishing this as industry best practice will make it more readily accepted by all stakeholders

Potential roadblocks and concerns raised

- Original draft included a proposal to also discontinue USP <87>
  - This has been taken out of scope of this phase of the work to ease the transition out of bioreactivity testing
- Use of USP Class VI compliant SUT may be written into regulatory filings for end users
  - This is understood to only be stated for DP container closure / control of materials, so the likely impact of the change is low
  - Inclusion in filings does not represent a major risk as FDA and USP have liaised and USP revision chapter has been updated
- Use of USP Class VI compliant SUT may be written into internal SOPs or buying specifications
  - This means there is likely to be some work required by anyone listing USP Class VI as a requirement (suppliers, integrators and end users)
- Phasing out the testing needs to be carefully managed by suppliers with adequate Change Notification to avoid disruptions in supply
- Need more support from end users to successfully implement the change



Evidence and reassurance around making the change

- SUT does not directly contact a patient and is only transiently in contact with the drug product

- Other existing testing methods provide more meaningful assurance of material safety
  - Low incidence rate of USP <88> failures suggests the test is not providing useful data
  - USP <87> is more sensitive to bioreactivity (Agar Diffusion Test, the Direct Contact Test, and the Elution Test)
  - Extractables testing provides qualitative and quantitative data on potentially hazardous substances present in the material
  - The BPSA Component Qualification Test Matrices list various standards that can be applied (physical, functional, chemical, biological and sterilization qualification)

- Plastics used in biopharmaceutical manufacturing are now well known, thoroughly characterised materials
  - Use of plastics is no longer a novel approach to biomanufacturing
  - Plastics suitable for medical devices and implants, in contact with the human body, should be risk-assessed as appropriate for drug manufacturing

- Release of USP <665>, specifically for single use plastics used in biopharmaceutical manufacturing, provides a standardized way of assessing SUT and does not include *in vivo* testing as a requirement

- Suppliers planning to discontinue USP <88> testing should follow their internal Change Notification procedures, ideally aligned with BioPhorum's Best Practice Guide

Activity to date

- USP88 working group established within BioPhorum's Sustainability Phorum
  - Activity started in March 2022 under SUS JLT
- Paper drafted by core authors
  - 5 representatives from 4 supplier companies
  - Content overview on next slide
- Paper in review by wider team
  - 17 representatives
  - 4 supplier companies
  - 7 end-user companies
- Educational webinar planned for 5th October
  - Supported by Pfizer & Sanofi
  - Looking for support from additional end user organizations

Overview of paper

Key focus

- **To accurately convey the current and historic landscape for bioreactivity testing for Single Use Technologies used in biomanufacturing, with the aim of uniting the industry in transitioning out of conducting *in vivo* testing on SUT**

Current state

- The post-Covid shift towards SUTs has allowed products to be brought to market faster by increased throughput, scalability and reduced risk of cross-contamination
- However, biocompatibility testing is required on plastics that come in to contact with drug product

Rationale for change

- Increased industry focus on more effective testing for plastics
- Regulatory changes to evaluation of common plastic materials for biomanufacturing (USP1663, 2017)
- Contract laboratories reluctant to carry out animal testing when materials are already deemed safe by pre-testing

Desired state and how to get there

- Achieve industry alignment on the use of alternative testing methods
- USP665 offers a standardized way of assessing and testing single-use materials
- Sustainability programs focusing on 3R or animal welfare initiatives also a key driver

Proposal

- Adopt a phased approach to change
- Start thinking about the change now
- Encourage widespread sharing of implementation plans and successes to drive a change to practice

Key messages and next steps

- *In vivo* bioreactivity testing (e.g. USP <88>) is not a regulatory requirement for SUT
- USP <88> testing does not provide meaningful quality or safety information over and above that which can be gained from alternative methods
- Many companies have Animal Welfare Initiatives or 3R programs, and targets to refine, reduce or replace animal testing where possible
  - These changes are part of sustainability programs, under the social responsibility category
- Commercial testing laboratories are declining requests to perform USP <88> unless it is absolutely essential (regulatory requirement)
- Suppliers transitioning out of this testing must follow best practice for managing the change to reduce disruption in the supply chain
- For new plastic materials, the industry should take a risk-based approach using a combination of USP <87> and extractables testing to determine safety
- Please contact Becky Tushingham at BioPhorum if you would like to support this important work and/or join the webinar (rebecca.tushingham@biophorum.com)

Thank you!

Q&A