BPSA Webinar:

The Modernization of Biological Reactivity Requirements for Single-Use Bioprocessing

November 6, 2025

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Our Panel of Industry Experts:

Monica Cardona
MilliporeSigma

James Hathcock
Cytiva

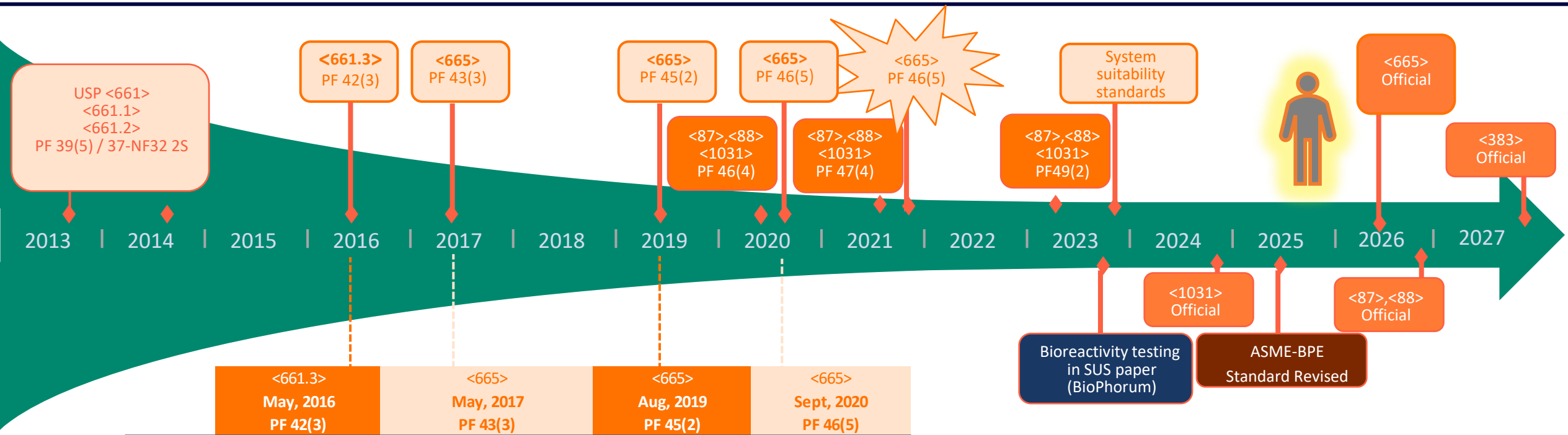
Paul Priebe
Paul M Priebe Consulting

James Vogel
The BioProcess Institute

What's Happening with Biocompatibility Requirements?

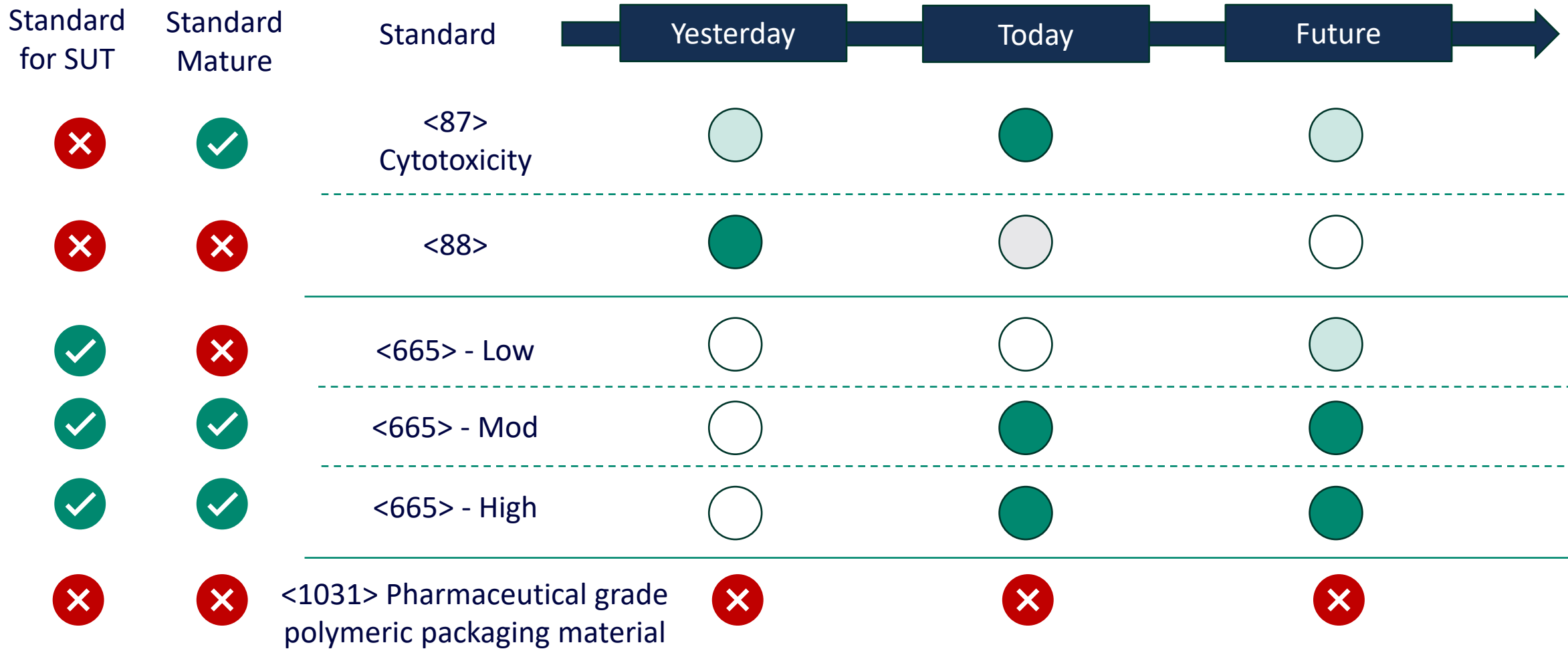
- **3Rs & Animal social welfare responsibility**
  - Is implanting single-use materials into animals the right things to do? Does it add scientific value? Does it align with application risk? Do we have a better understanding and tools than 20+ years ago?
- **USP <88> changes and elimination of plastics classification**
  - Supplier documentation impact? Biomanufacturer RFPs impact? Future change controls?
- **USP <87> changes**
  - Should I be asking for these new tests?
- **USP <1031> changes**
  - Does this apply to single use? Should I claim 'Pharmaceutical Grade Polymeric Packaging Materials'?
- **How do I reference the old vs new chapters?**

Changing Expectations for Biological Reactivity



		<661.3> May, 2016 PF 42(3)	<665> May, 2017 PF 43(3)	<665> Aug, 2019 PF 45(2)	<665> Sept, 2020 PF 46(5)
Risk	Low	<87>	<87>	None	Out of Scope
	Moderate	<87> + <88>, Class VI	<87> + <88>, Class VI	<87>	Out of Scope
	High	<87> + <88>, Class VI	<87> + <88>, Class VI	<87> + <88>, Class VI	Out of Scope

Direction We are Moving



What is Changing with <87>, <88> and <1031>?

USP Pharmaceutical Packaging and Delivery Systems

Let's Talk about SCOPE!

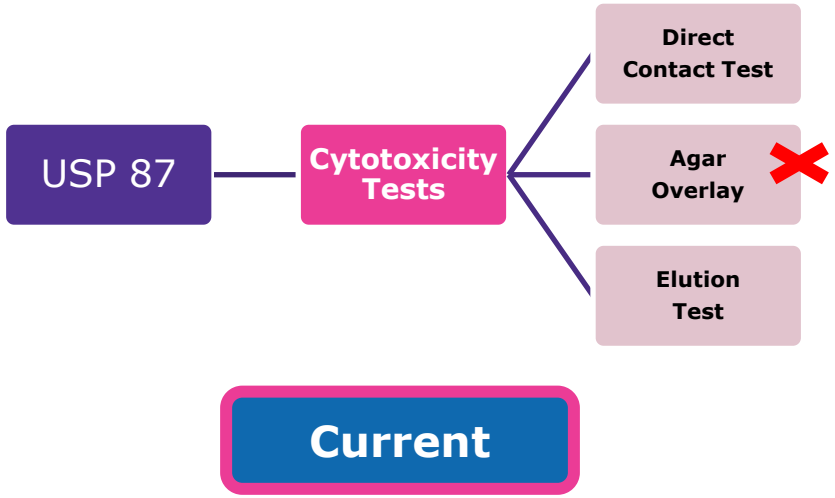
- <87> & <88> compendial standards for biological reactivity testing of elastomeric plastics and other polymeric materials are focused on **drug product packaging** (i.e., primary container closures) and **delivery systems** (e.g., syringes, auto-injectors, inhalers, intravenous systems).

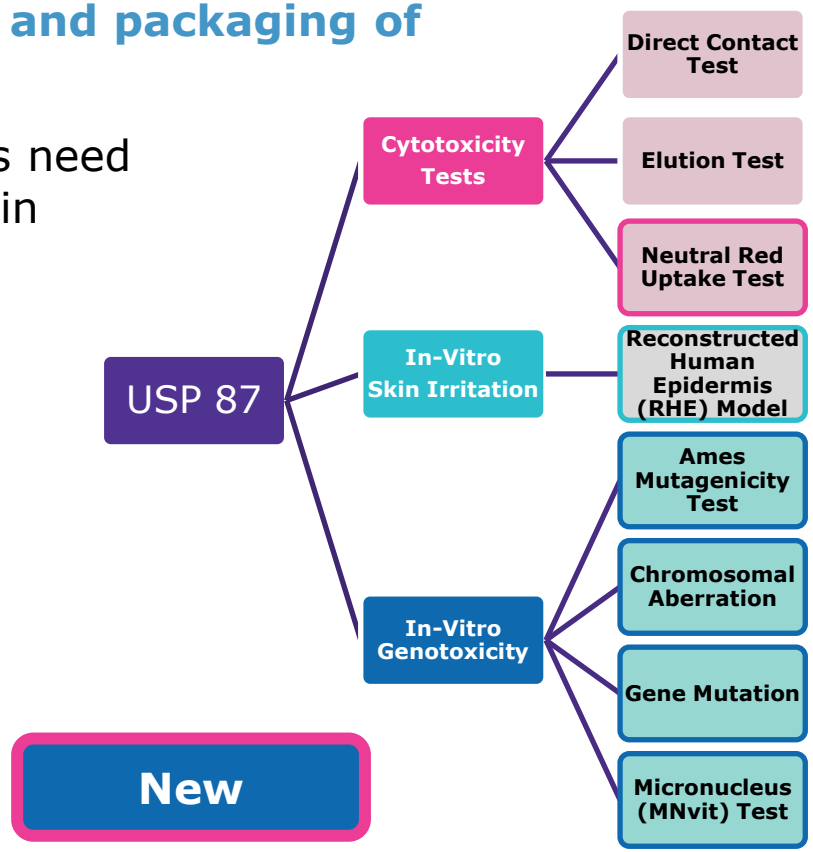
- Plastics used in pharmaceutical manufacturing systems, such as filters and Single-Use Technologies, **are out of scope** of the referenced bioreactivity testing standards.

- Because of a lack of any specific standards for manufacturing systems, the industry has historically implemented **USP <88>, Class VI for both filters and Single Use Technology**.

USP 87 Biological Reactivity Tests In-Vitro (December 2026)

- **Scope** : "The in vitro tests described in this chapter are designed to determine the biological response of cells to extracts of elastomers, plastics and other polymeric materials used **in packaging and delivery systems for drugs and packaging of combination products"…..**
- Beginning December 2026, to claim complete USP 87 , materials need to be tested for *In-Vitro* Skin Irritation and *In-Vitro* Genotoxicity in addition to one of the three *In-Vitro* Cytotoxicity Test options.

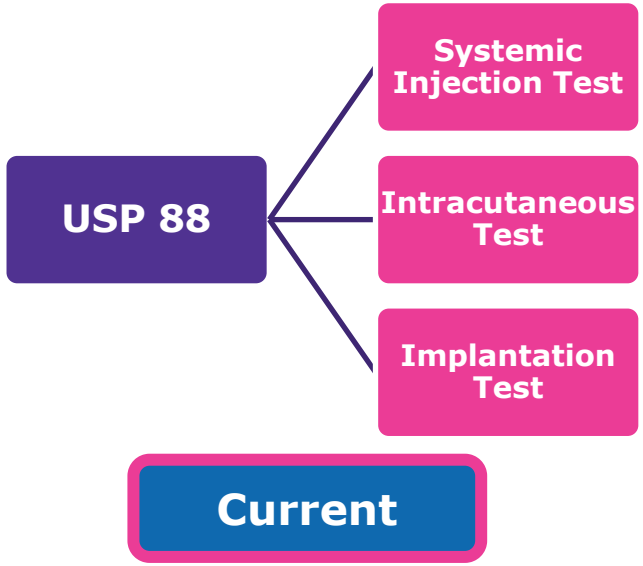


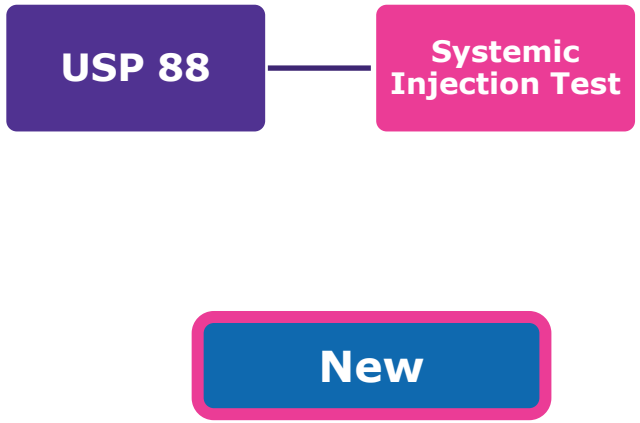


USP 88 Biological Reactivity In Vivo (December 2026)

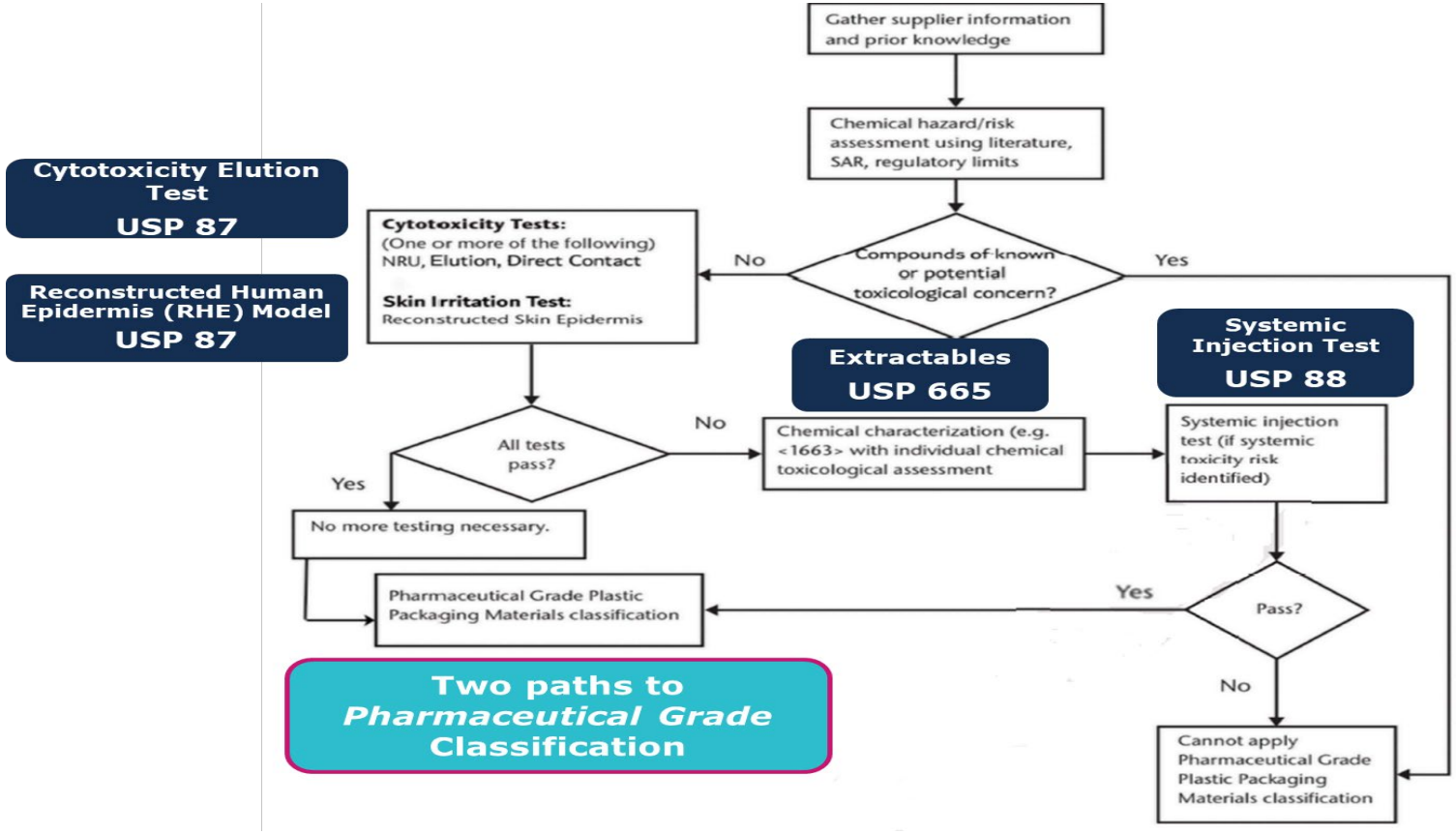
- This chapter describes the ***Systemic Injection Test*** designed to determine the biological response of animals to elastomers, plastics and other polymeric materials or their extracts used in **packaging systems for drugs and packaging of combination products**.

- All single use components that today claim **USP 88 Class VI** , meet the ***System Injection Test*** in addition to the **Intracutaneous and Implantation** (Intramuscular or Subcutaneous) Tests which are no longer required.





USP <1031> Decision Tree – Packaging Focused



USP 1031 The Biocompatibility of Pharmaceutical Packaging Systems & Their Materials of Construction (December 2026)

- The purpose of this chapter is to provide guidance for biocompatibility evaluation of polymeric materials of construction and polymeric components for **pharmaceutical packaging systems.** Background information and principles for the application of Biological Reactivity Tests, *In Vitro* (USP 87) and *In Vivo* (USP 88) are provided.

- The term "***Pharmaceutical Grade Polymeric Packaging Materials***" replaces the Classification of Plastics Classes I-VI in USP 88 .

- To obtain the ***Pharmaceutical Grade classification*** the material must pass :

1 Cytotoxicity Test +
***In Vitro* Skin Irritation Test**

OR

Chemical Characterization, USP 665??
Toxicological Assessment +
USP 88 Systemic Injection Test

- Suppliers claiming USP 87 today, generally do so by the ***Cytotoxicity Elution Test*** which is comparable to ISO 10993-5.

- Most suppliers traditionally claimed ***USP 88 Class VI***, so they already have the ***Systemic Injection data.***

Considerations – USP 87

Test	QTY	Total Test Cost
Cytotoxicity Tests		
3.3 Direct Contact Test	1	**$1,300**
3.4 Elution Test	1	$800
3.5 Neutral Red Uptake (NRU) Test	1	TBD
In- Vitro Skin Irritation		
4.1 Reconstructed Human Epidermis (RHE) Test	1	$4,000
Pharmaceutical Grade Claim Cost	**1**	**$5,300**
In- Vitro Genotoxicity Tests		
5.2 Ames Bacterial Reverse Mutation Assay	1	$5,000
5.3.1 Chromosomal Aberration Test	1	$25,000
5.3.2 Gene Mutation Test	1	$50,000
5.3.3 Micronucleus (Mnvit) Test	1	$45,000
In-Vitro Genotoxicity Test Cost		**$120,000**
Total USP 87 Claim Cost	**1**	**$126,000**

How Do We Move Forward

USP <87> or <88>?

<381> Elastomeric Components in Injectable Pharmaceutical Product Packaging/Delivery Systems
(to be official 01DEC2025)

Applies to
- ☑ Primary packaging
- ☐ Single-use (manufacturing components)

4.1 Biological Reactivity:

4.1 Biological Reactivity: Elastomeric components (Type I and Type II) meet the requirements of *Biological Reactivity Tests, In Vitro* ⟨87⟩.[1] If components do not meet the requirements of ⟨87⟩, they can be subjected to in vivo testing set forth in *Biological Reactivity Tests, In Vivo* ⟨88⟩. Components that meet the requirements of ⟨87⟩ are not required to undergo ⟨88⟩ testing.

Type I and Type II closures must both conform to the requirements of either the in vitro or the in vivo biological reactivity tests.

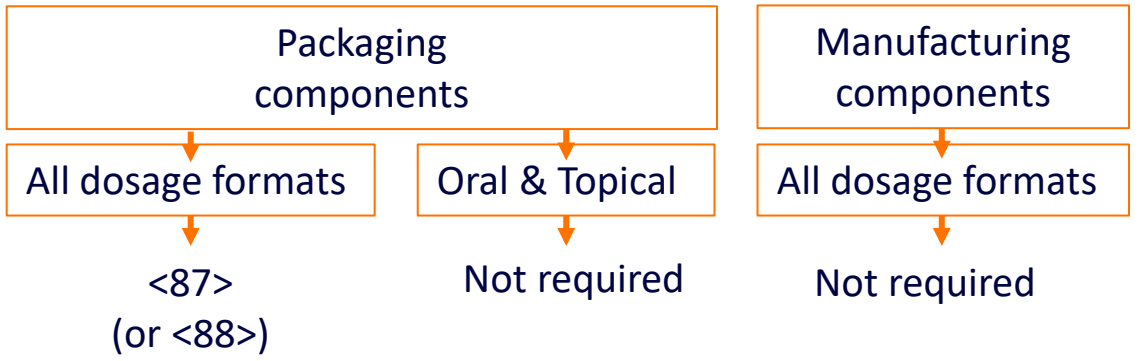
Acceptance criteria: Test selection and results are consistent with ⟨87⟩ and/or ⟨88⟩.

… must conform to the requirements of either the *in vitro* **or** the *in vivo* biological reactivity tests.

<383> Cured Silicone Elastomers for (Bio)pharmaceutical packaging and manufacturing components
(to be official 01DEC2027)

Applies to
- ☑ Primary packaging
- ☑ Single-use (manufacturing components)

Biological Reactivity: Table 1

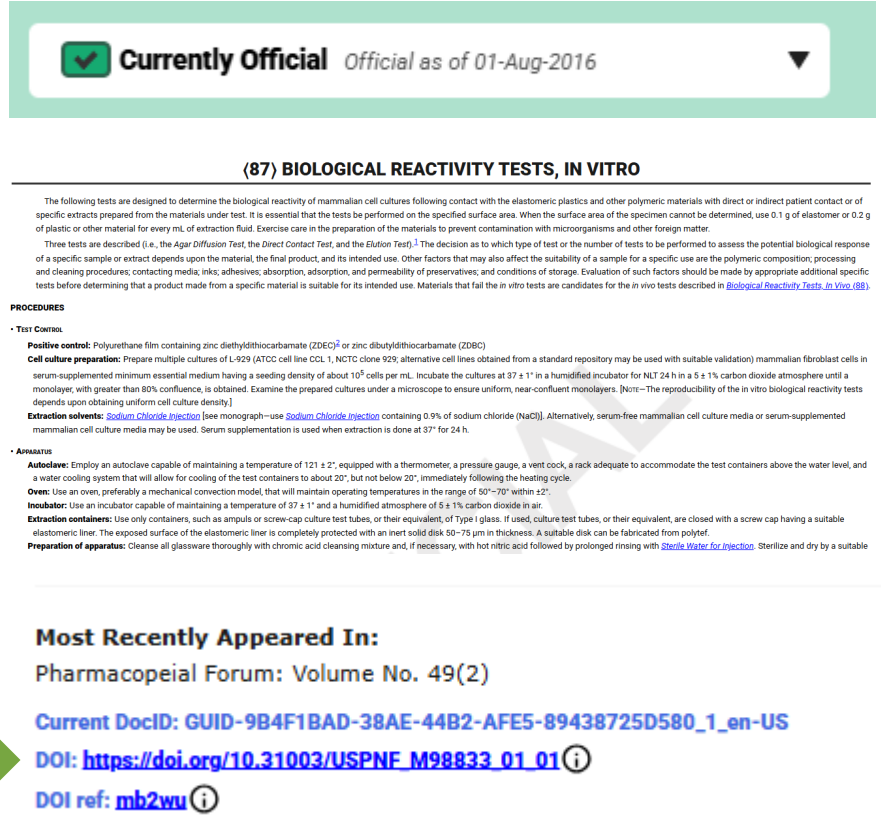


Moving Forward

Legacy Components (<2025)	Newly Launched components (>2026)	Future Direction
Biocompatibility + USP <87> Cytotoxicity or ISO 10993-5 **OR** + USP Class/VI or ISO 10993 6, 10/23, 11	**Biocompatibility** + [a]USP <87> Cytotoxicity or ISO 10993-5 x USP <87> Sensitization x USP <87> Genotox *[a]USP <87>. In the event of a failure, USP <88> can be used*	**Biocompatibility** + [a]USP <87> Cytotoxicity, ISO 10993-5 **OR** + ASTM E3231, or + Compendial compliance (e.g., EP 3.1.9), or + Reach Compliance (?) **OR**
Chemical Suitability + USP <665> L/M/H ❖ Very low risk (e.g. SA<<1% or 0.1 SA/V) ❖ Other compendia satisfaction (e.g., 87, 88 383, 661, EP 3.1.9, etc)	**Chemical Suitability** + USP <665> L/M/H ❖ Need <665> Low Risk Acceptance Criteria Alignment	**Chemical Suitability** + USP <665> L/M/H
Pharmaceutical Plastic x Not appropriate to SUT	**Pharmaceutical Plastic** x Not appropriate to SUT	**Pharmaceutical Plastic** x Not appropriate to SUT

Both are acceptable

Referencing USP Chapter Versions



Currently Official *Official as of 01-Aug-2016*

⟨87⟩ BIOLOGICAL REACTIVITY TESTS, IN VITRO

The following tests are designed to determine the biological reactivity of mammalian cell cultures following contact with the elastomeric plastics and other polymeric materials with direct or indirect patient contact or of specific extracts prepared from the materials under test. It is essential that the tests be performed on the specified surface area. 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. Exercise care in the preparation of the materials to prevent contamination with microorganisms and other foreign matter.

Three tests are described (i.e., the *Agar Diffusion Test*, the *Direct Contact Test*, and the *Elution Test*).[1] The decision as to which type of test or the number of tests to be performed to assess the potential biological response of a specific sample or extract depends upon the material, the final product, and its intended use. Other factors that may also affect the suitability of a sample for a specific use are the polymeric composition; processing and cleaning procedures; contacting media; inks; adhesives; absorption, adsorption, and permeability of preservatives; and conditions of storage. Evaluation of such factors should be made by appropriate additional specific tests before determining that a product made from a specific material is suitable for its intended use. Materials that fail the *in vitro* tests are candidates for the *in vivo* tests described in *Biological Reactivity Tests, In Vivo ⟨88⟩*.

PROCEDURES

• **Test Control**

Positive control: Polyurethane film containing zinc diethyldithiocarbamate (ZDEC)[2] or zinc dibutyldithiocarbamate (ZDBC)

Cell culture preparation: Prepare multiple cultures of L-929 (ATCC cell line CCL 1, NCTC clone 929; alternative cell lines obtained from a standard repository may be used with suitable validation) mammalian fibroblast cells in serum-supplemented minimum essential medium having a seeding density of about 10^5 cells per mL. Incubate the cultures at 37 ± 1° in a humidified incubator for NLT 24 h in a 5 ± 1% carbon dioxide atmosphere until a monolayer, with greater than 80% confluence, is obtained. Examine the prepared cultures under a microscope to ensure uniform, near-confluent monolayers. [Note—The reproducibility of the in vitro biological reactivity tests depends upon obtaining uniform cell culture density.]

Extraction solvents: *Sodium Chloride Injection* [see monograph—use *Sodium Chloride Injection* containing 0.9% of sodium chloride (NaCl)]. Alternatively, serum-free mammalian cell culture media or serum-supplemented mammalian cell culture media may be used. Serum supplementation is used when extraction is done at 37° for 24 h.

• **Apparatus**

Autoclave: Employ an autoclave capable of maintaining a temperature of 121 ± 2°, equipped with a thermometer, a pressure gauge, a vent cock, a rack adequate to accommodate the test containers above the water level, and a water cooling system that will allow for cooling of the test containers to about 20°, but not below 20°, immediately following the heating cycle.

Oven: Use an oven, preferably a mechanical convection model, that will maintain operating temperatures in the range of 50°–70° within ±2°.

Incubator: Use an incubator capable of maintaining a temperature of 37 ± 1° and a humidified atmosphere of 5 ± 1% carbon dioxide in air.

Extraction containers: Use only containers, such as ampuls or screw-cap culture test tubes, or their equivalent, of Type I glass. If used, culture test tubes, or their equivalent, are closed with a screw cap having a suitable elastomeric liner. The exposed surface of the elastomeric liner is completely protected with an inert solid disk 50–75 µm in thickness. A suitable disk can be fabricated from polytef.

Preparation of apparatus: Cleanse all glassware thoroughly with chromic acid cleansing mixture and, if necessary, with hot nitric acid followed by prolonged rinsing with *Sterile Water for Injection*. Sterilize and dry by a suitable

Most Recently Appeared In:

Pharmacopeial Forum: Volume No. 49(2)

Current DocID: GUID-9B4F1BAD-38AE-44B2-AFE5-89438725D580_1_en-US

DOI: https://doi.org/10.31003/USPNF_M98833_01_01

DOI ref: mb2wu

[USP referencing-guideline-10-14-21-final.pdf]

Background:

As USP has transitioned the *USP-NF* from print to an online-only product the general publication reference (e.g. *USP41–NF36_1S*) will no longer be an indication of an official period. Although USP will continue to publish the *USP–NF* standards on a set schedule, there are changes in the document-centric platform that affect the application of official date references. Each individual document within the new online publication has its own official date reference, which is linked to a unique permanent Digital Object Identifier (DOI) available in November 2021 with the launch of USP-NF 2022 Issue 1. The DOI will only change when there is a revision to a document.

Citation Examples

- **General Chapter:** USP. Injections and Implanted Drug Products (Parenterals)—Product Quality Tests <1>. In: USP–NF. Rockville, MD: USP; Dec 1, 2020.
  DOI: https://doi.org/10.31003/USPNF_M98730_03_01.
- **Monograph:** USP. Acebutolol Hydrochloride. In: USP–NF. Rockville, MD: USP; May 1, 2021.
  DOI: https://doi.org/10.31003/USPNF_M125_05_01.

Alignment on Referencing USP Chapter Versions

Current State Examples

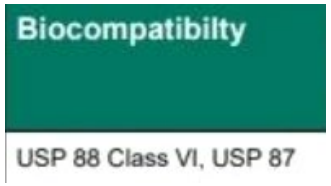
1 **Materials of Construction**

The fluid contact components of the Allegro system have met the requirements for biological reactivity, in vivo, under the **United States Pharmacopeia** (USP <88>) for Class VI plastics.

3 **Materials of Construction**

All polymeric components in contact with process fluids meet requirements for biological reactivity: United States Pharmacopeia (USP) <87>, USP <88> (Class VI), ISO 10993-5, or ISO 10993-6, 10/23, and 11.

2



These types of references may be confusing for many readers

What's Needed (>2025)

Full reference

- USP <87> DOI: 10.31003/USPNF_M98833_01_01
- USP <87> cytotoxicity DOI: 10.31003/USPNF_M98833_02_01
- USP <88> / Class VI DOI: 10.31003/USPNF_M98834_01_01
- USP <665> - Moderate DOI: 10.31003/USPNF_M11135_03_01

Short reference

- USP <87> DOI: mb2wu
- USP <87> cytotoxicity DOI: ow8df
- USP <88> / Class VI DOI: u4inx
- USP <665> - Moderate DOI: 77w5m

Effective Dates

Currently Official *Official as of 01-Aug-2016*

Not Yet Official *To be Official on 01-Dec-2026*

Currently Official *Official as of 01-Aug-2013*

RB **Not Yet Official** *To be Official on 01-May-2026*

How are USP Changes Being Referenced in ASME-BPE?

ASME-BPE History

- The ASME BPE has historically referenced the USP and ISO for Biocompatibility testing of Polymeric materials and components (Seals, Gaskets, Single-use). Both
  - In vitro (in Glass, (USP <87> (or ISO 10993-5)) **and**
  - In vivo (in Animal (USP <88> Class VI (or ISO 10993-6, -10, and -11)
- There were no specific tests designed for BioProcess Equipment available, and it was felt that Food requirements such as CFR 177 were not detailed enough for the BioPharmaceutical applications utilizing the BPE.

ASME BPE Biocompatibility Update for 2026

- The ASME BPE reviewed the situation and approved an update to the requirements for plastic materials and components used in manufacturing operations to align with
  - USP<665> (effective May 2026) and the
  - Biophorum Paper for components and systems used for the manufacture of pharmaceuticals,
  - (not pharmaceutical packaging/delivery systems or medical devices).

ASME BPE Biocompatibility Update for 2026

- The ASME-BPE updates consist of 19 changes across 6 Parts and 3 Appendices. The changes were divided into four ballots for four subcommittees. Approved for 2026 publication They are:
  - Update the requirement of Biocompatibility testing to be in vitro cytotoxicity only. Other in vitro and in vivo (animal) testing is not required and should be avoided, unless it is justified in the context of suitability for the intended use (e.g. toxicological assessment.)
  - Past in vivo test results from applicable past tests may be acceptable to meet the biocompatibility testing requirement.
  - Consolidate all Biocompatibility references to refer to section PM 3.1.
  - Remove all Class VI references.

ASME BPE Biocompatibility USP<665>

- USP<665> Clearly states the following:
  - *Introduction: To ensure that plastic materials and components used in manufacturing operations are suitable for their intended use, they should be:*
  - *Composed of components that are suitable for use and compatible with biopharmaceutical DSs, pharmaceutical or biopharmaceutical DPs, and all process intermediates and/or process streams.*
  - *Single-Use and Multi-Use*
  - *Functional. (Out of Scope)*

- Commentary:
  A Clear scope for USP<665> and its applicability to ASME BPE

ASME BPE Biocompatibility 2026 Update Strategy

- All BioProcess Equipment
  - Multi-Use and Single-Use
  - Thermoplastics and Thermoset Elastomers
- USP<665>-
  - plastic materials and components used in manufacturing operations are suitable for their intended use
  - biocompatibility testing as an alternate qualification procedure,
- USP<381>-Elastomers
  - Referenced in USP<665>
  - Requirements may apply to manufacturing operations
  - Biocompatibility USP<87> Cytotoxicity Elution

ASME BPE Biocompatibility 2026 Update

PM-3.1.1 Biocompatibility Testing

- Polymeric component/material manufacturers,
- Thermoplastic and thermoset elastomer materials,
- **In vitro biocompatibility testing per the United States Pharmacopeia USP Biological Reactivity Tests, In Vitro Chapter <87> Cytotoxicity tests (or ISO 10993-5).**
- Other biocompatibility tests for polymeric materials may be required per a suitability evaluation to determine the fitness of the component/material for its intended use

ASME BPE Biocompatibility 2026 Update

PM-3.1.1 Biocompatibility Testing

- Avoid conducting new in vivo tests unless required by suitability evaluation.
- Previous in vivo test results may be deemed acceptable to fulfill the biocompatibility testing requirement.
- Testing article shall be representative of the combination of the materials, components, and manufacturing processes (e.g. bracketing approach).
- Biocompatibility shall be reassessed for significant changes in raw materials or manufacturing processes. Otherwise, biocompatibility testing is performed during initial qualification of the material and process by the component supplier/manufacturer.

ASME BPE Biocompatibility 2026 Update

- 19 changes across 6 Parts and 3 Appendices are Approved

✓**Approvals complete in 2025**

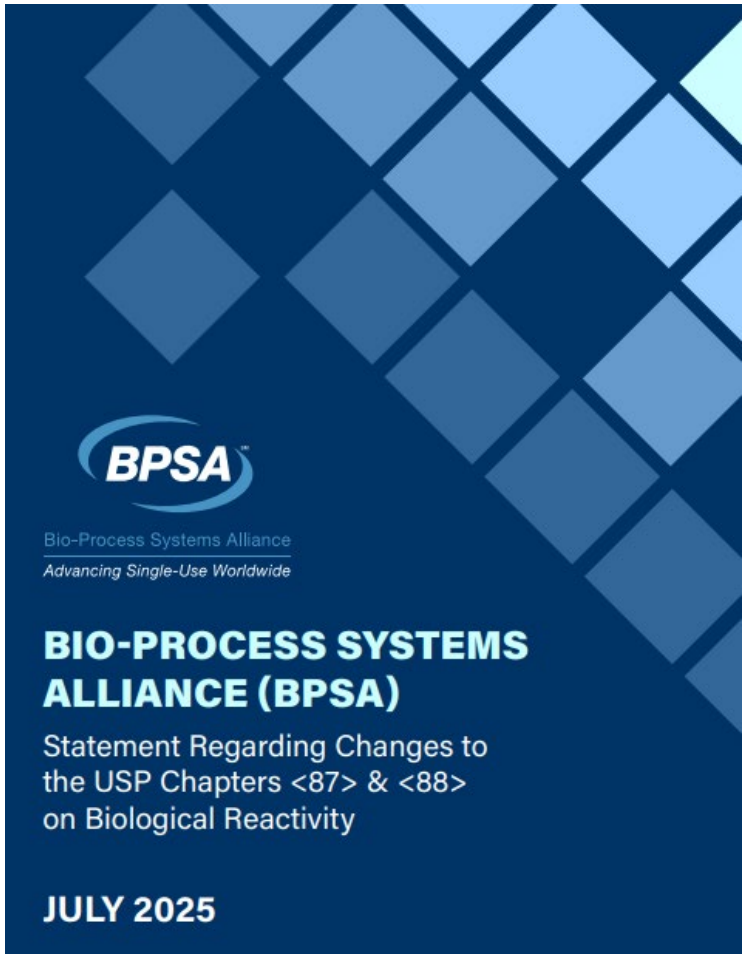
- 2026 BPE Edition update with the editor
- Publishing in 2026

Bio-Process Systems Alliance Statement Regarding Changes to the USP Chapters <87> & <88> on Biological Reactivity

Bio-Process Systems Alliance (BPSA) Statement Regarding Changes to the USP Chapters <87> & <88> on Biological Reactivity

- Issued by the: BPSA Scientific Advisory Council (SAC)

To download, visit our technical guides library at bpsalliance.org or scan here:



BPSA Statement Regarding Changes to the USP Chapters <87> & <88> on Biological Reactivity

BPSA supports these changes in the ASME-BPE and recommends that suppliers do the following to ensure proper evaluation of Single-Use Materials and components during the transition period of 2025 and 2026.

BPSA Statement Regarding Changes to the USP Chapters <87> & <88> on Biological Reactivity

New Components-Baseline Single Use Technology (SUT)fluid-contact material testing expectations for new components from Dec 2025 onward:

- Biocompatibility: USP <87> Cytotoxicity Elution or ISO 10993-5 is the default Biocompatibility/Bioreactivity Test for SUT.
  - USP <87> sensitization, <87> genotoxicity added where supplier deems appropriate, but not default expectation. This may be reviewed further at a future date.
  - USP <88> Animal Implantation, Intracutaneous Tests and Systemic Injection Tests (only after December 2026), OR ISO 10993 equivalents are not appropriate for most SUT. Testing should be only by exception with justification.
- Extractables: testing per USP <665> low, moderate, or high
  - Note: USP <665> low risk testing not well-accepted to date, and may require future guidance from USP/industry to be meaningfully applied
  - BioPhorum extractables: considered advantageous to many end user and may be performed by suppliers to enhance their product offering. It is not considered a compendia or core regulatory requirement.

BPSA Statement Regarding Changes to the USP Chapters <87> & <88> on Biological Reactivity

Legacy Components-Baseline SUT fluid-contact material testing expectations for legacy components launched prior to Dec 2025 (FYI only).

- Biocompatibility: USP Class VI OR USP <87> OR ISO 10993 equivalents. i.e. – historical cytotoxicity testing or USP <88>/Class VI testing or the ISO 10993 equivalents are deemed satisfactory to meet the Biocompatibility/Bioreactivity requirements.
- Extractables: Whereas various practices have been used for extractables, the expectation is that all components will eventually be assessed and tested as appropriate to USP <665> by the suppliers, prioritizing testing on components associated with the highest risk (e.g.- high surface area, large surface area to process volume ratio, used in late downstream processing, etc).

BPSA Statement Regarding Changes to the USP Chapters <87> & <88> on Biological Reactivity

Pharmaceutical Grade Plastics Ontology.

- The term "**Pharmaceutical Grade Plastics**" is mentioned in the new version of the USP<87> and USP<88>.

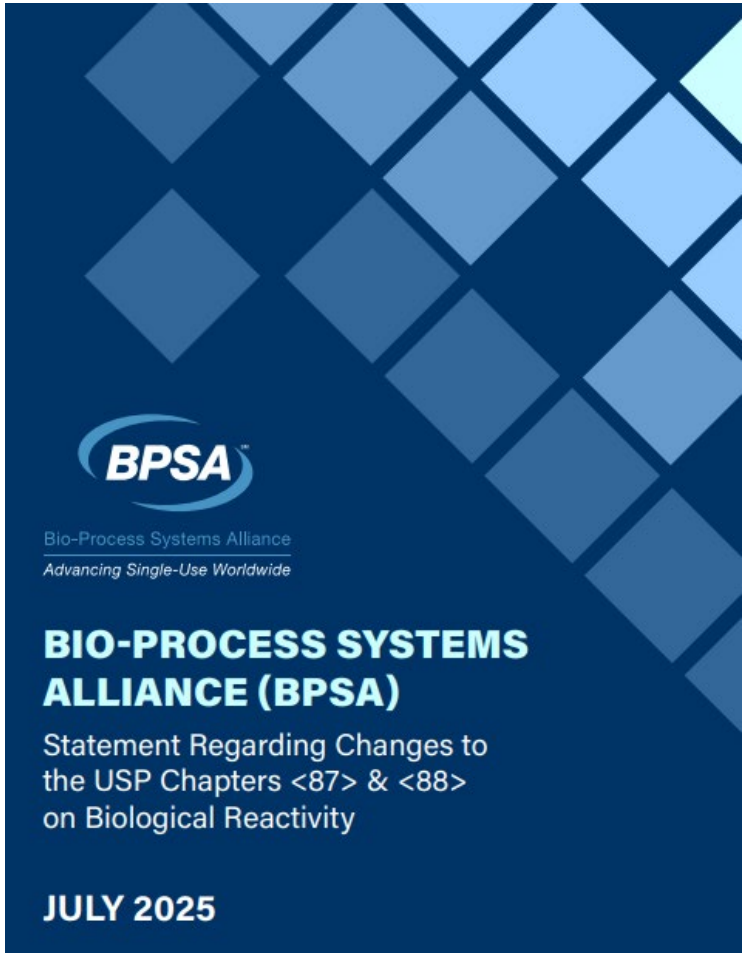
- The term is specified for container systems only and **does not apply to single-use bioprocessing.**

BPSA Statement Regarding Changes to the USP Chapters <87> & <88> on Biological Reactivity

- To download BPSA's statement, visit our technical guides library at bpsalliance.org.

Next steps:

- The Biocompatibility reference of the **BPSA Quality Test Matrices** will be updated accordingly and will continue to ensure proper alignment of Single-Use Standards and Requirements.



Moving Forward

Legacy Components (<2025)	Newly Launched components (>2026)	Future Direction
Biocompatibility + USP <87> Cytotoxicity or ISO 10993-5 **OR** + USP Class/VI or ISO 10993 6, 10/23, 11	**Biocompatibility** + [a]USP <87> Cytotoxicity or ISO 10993-5 x USP <87> Sensitization x USP <87> Genotox [a]*USP <87>. In the event of a failure, USP <88> can be used*	**Biocompatibility** + [a]USP <87> Cytotoxicity, ISO 10993-5 **OR** + ASTM E3231, or + Compendial compliance (e.g., EP 3.1.9), or + Reach Compliance (?) **OR**
Chemical Suitability + USP <665> L/M/H ❖ Very low risk (e.g. SA<<1% or 0.1 SA/V) ❖ Other compendia satisfaction (e.g., 87, 88 383, 661, EP 3.1.9, etc)	**Chemical Suitability** + USP <665> L/M/H ❖ Need <665> Low Risk Acceptance Criteria Alignment	**Chemical Suitability** + USP <665> L/M/H
Pharmaceutical Plastic x Not appropriate to SUT	**Pharmaceutical Plastic** x Not appropriate to SUT	**Pharmaceutical Plastic** x Not appropriate to SUT

Both are acceptable

Q&A Discussion

Please submit your questions through the Q&A feature.

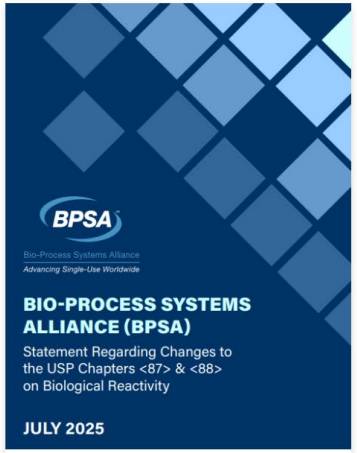
Thank You!

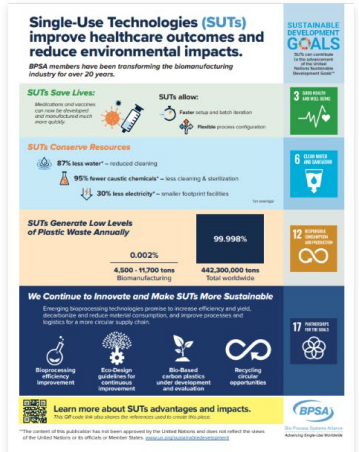
For questions, contact:

bpsa@socma.org

For additional BPSA resources, visit:

bpsalliance.org/resources





20 YEARS
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Advancing Single-Use Worldwide

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Upcoming Events

- November 17, 2025 | BPSA Webinar
  Sustainable Bioprocessing with SUTs: Data, Practices & Innovations
- December 2-3, 2025 | Lyon, France
  A3P & BPSA Single-Use Conference
- *Save the Date!* July 27–29, 2026 | Boston, MA
  BPSA International Single-Use Summit