**The Biopharmaceutical Process Extractables Core Team**

# Evaluation of Extractables from Product-Contact Surfaces

**Potential interactions between a drug product and its packaging or container closure have always been important considerations for parenteral manufacturers. Now — at a time of increased regulatory interest in extractables, lower limits of detection, and more biopharmaceuticals reaching commercial stage — the consequences of not evaluating the extractables in your process stream can be significant. Participants from more than 15 biopharmaceutical companies and data collected for more than 25 years were used to develop the parameters of this article.**

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The quality of state-of-the-art materials has improved considerably during the past 25 years. However, it is known that all processing systems can release insoluble or soluble materials into a product process stream. The insoluble material is usually called particulate contamination, and the soluble substances are called *extractables.* (Italicized words are defined in the "Definitions for Evaluating Extractables" sidebar.) New, lower-extractable, higher-quality materials are now being used. At the same time, analyses of extractables from product-contact materials have significantly reduced limits of detection.

In the past, the evaluation of extractables from *product-contact surfaces* has focused mainly on container closure systems because of the extended duration of product contact in final containers. Expanding the range of extractables evaluation into the product *process stream* is the next logical extension of that knowledge base.

This article offers a science-based approach for evaluating potential extractables from product-contacting equipment surfaces during pharmaceutical production. The article is limited to pharmaceutical production equipment designed to manufacture biopharmaceutical *Active Pharmaceutical Ingredients* (APIs) for use in parenteral products. Final container and closure surfaces are not included.

We intend to provide a starting point for companies when they are generating their own materials evaluation programs. This article is not intended to define an industry standard for such a program.

## Biopharmaceutical Process Extractables Core Team

The suggestions in this article were reached by consensus by representatives from several pharmaceutical and biotechnology companies. Two Biopharmaceutical Process Extractables Summits were held for interested parties — on 12 April 2002 and 7 June 2002. The summits were hosted by **Sid Wolfe** at Chiron Corporation with **Bob Seely** and **Don Miller** acting as group leaders.

The emphasis of those meetings was on how the process stream and its equipment influenced the extractables during production — from in-process materials to final formulated bulk product. The summits did not address container closure systems because that topic has been extensively covered in other venues.

The data in this article were generated over a 25-year period at the Bayer Corporation laboratories in Berkeley, CA, and Clayton, NC.

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### Regulating Extractables

The *Code of Federal Regulations* (CFR) and regulations from the International Committee on Harmonisation (ICH) mandate that equipment and materials used in the manufacture of drugs and biologics should not alter the safety, identity, strength, quality, or purity of a drug product:

CFR Title 21, Part 211.65 states

> Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements. (1)

The ICH API GMPs, Part 5.11 states

> Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications. (2)

To ensure compliance with these regulatory requirements, an evaluation for potential extractables should be performed on the materials in the manufacturing process stream. Upstream surfaces (that is, materials upstream of the final container and closure surfaces) pose significantly less risk to product quality or patient safety because of the shorter product-contact time, the low levels of extractables anticipated, and the many routes for removing those extractables during purification. However, each of those surfaces should be evaluated to ensure that acceptable materials are being used.

The approach we take in this article — an approach for implementing an extractables evaluation program — was reached by consensus and deemed reasonable by representatives from several pharmaceutical and biotechnology companies (see the "Core Team" box for primary authors and information on the Extractables Summit). The evaluation program we offer includes our scientific rationale, the systematic

### Definitions for Evaluating Extractables

These definitions relate specifically to the evaluation of extractables from product-contact surfaces.

**Active Pharmaceutical Ingredient (API).** Also referred to as "drug substance." Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that when used in the production of a drug becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to effect the structure and function of the body (2).

**Chemically defined material.** A chemically defined material is one specified by the manufacturer to meet the specifications for a particular catalog number, or a material that meets a pharmaceutical compendial specification, or a material that consistently meets an internal specification for identity, assay, and at least one primary impurity.

**Colony forming units (CFU).** Usually given as CFU/g or CFU/mL; a measurement of the undifferentiated cells in a test culture.

**Compendial sources.** Organizations that establish standards and specifications to ensure the quality of medicines for human and veterinary use.

**European Pharmacopoeia (EP).** A standards organization whose recommendations and monographs are honored by regulatory agencies.

**Extract.** A solution that contains solvent and extractables.

**Extractables.** Small quantities of chemical compounds and elements, not intentional components of the process stream, that are capable of being extracted by product-containing solutions from the surfaces of pharmaceutical production process equipment.

**Extractant.** A solvent used to extract a substance.

**High-risk materials.** Materials which, through a combination of close proximity to the final container in the process stream, high surface area, and high extractables or toxicity potential, can threaten the quality, or present potential safety risks, to a drug product.

**Human serum albumin (HSA).** Major blood-borne protein used in many cell-culture processes.

**Incoming inspection document.** Acceptance or rejection criteria for incoming materials; maintenance of appropriate documents on incoming tests, inspections, or other means of verification.

**Inductively coupled plasma (ICP).** A technique for analyzing samples, usually from aqueous solutions, to detect very low levels of elements in a sample.

**Japanese Pharmacopoeia (JP).** A standards organization whose recommendations and monographs are honored by regulatory agencies.

**Materials safety evaluation group.** The department or people who set materials specifications and evaluate testing results to determine if materials are safe for use in pharmaceutical processes.

**Minimum essential medium (MEM).** A cell culture medium well-suited for many mammalian cells when used with a serum supplement.

**Model solvent.** A pure solvent, which mimics the process solution in its extraction capability (for example, water or ethanol).

**Model solvent extraction.** An extraction method performed on a material using a model solvent, in the absence of product, to generate potential extractables for quantifying and testing.

**Process stream.** The combination of steps from the beginning (often fermentation) to the end (final container filling) of the manufacturing process.

**Product.** Any solid or liquid in the manufacturing process that contains the product molecule.

**Product-contact surface.** Any surface in the process stream contacting a solution containing product molecules.

**Pyrogen.** A substance that causes fever.

**Residue on ignition-inductively coupled plasma.** ROI-ICP.

**Total organic carbon (TOC).** A measure of the amount of organic materials suspended or dissolved in water.

**United States Pharmacopeia (USP).** A standards organization whose recommendations and monographs are honored by regulatory agencies.

## Examples of Test Protocols

The following test protocols are for plastics and elastomers that are frequently used in aqueous-based processes.

### Sample Preparation

**Sample preparation for polymers.** Obtain pellets, film, or filter membranes for extraction or use formed parts that are used in the manufacturing process.

- *For pellets*, calculate the surface area of a typical pellet, weigh 10 pellets, and calculate the surface area for that weight, then calculate the weight for 6,000 $cm^2$. Rinse the pellets twice in purified water before placing in a liter of purified water[a] for extraction. Stir with a Teflon-coated magnetic stirring bar. Run a purified water control, and subtract out any background.
- *For elastomer slabs*, obtain 6 × 6-inch ASTM slabs cured and postcured exactly as the product will be for extraction studies. Cut 6,000 $cm^2$ of the slabs in at least eight sections for easy circulation, or use formed parts that are used in the manufacturing process. Rinse the elastomer slab twice in purified water before placing in a liter of purified water for extraction[a]. Stir with Teflon-coated magnetic stirring bar. Run a purified water control, and subtract out any background.
- *For formed parts*, discuss with the manufacturer of the molded part any mold release or other processing agents that the vendor might use. Ensure that such agents are removed by the manufacturer or by your pretreatment process. Ascertain the water quality the manufacturer uses. City water contains high level of pyrogens.

### Extraction Tests

**Extraction test conditions.** Current USP extraction conditions require that the test article be extracted in purified water at a test article surface area of 6,000 $cm^2$ per liter of purified water at 70 °C for 24 hours.

**Tests on purified water[a] extracts** should include:

- pH
- conductivity
- *total organic carbon (TOC)*
- nonvolatile residue
- ultraviolet (UV) scan
- *MEM* elution cytotoxicity (USP) method (Make purified water extract isotonic, adjust pH to 6.8–7.2, and steam sterilize at 121 °C for 30 minutes before testing.)
- pyrogen (if appropriate)
- other USP tests (if appropriate)

**Tests on solid materials** should include:

- ROI followed by emission spectrographic analysis, ICP, or atomic absorption for heavy metals
- microbial load (if appropriate)
- MEM elution cytotoxicity (USP) using 5% *HSA* and extracting at 6,000 $cm^2$/L on steam-sterilized (three drops of water) sample for seven days at 50 °C
- USP physicochemical tests (if desired)
- other tests (such as HPLC analysis of residues)

[a]Drug product vehicles or process intermediates are also candidates as extraction media. These tests, which specify purified water, will not function using buffers or other organic compounds. The tests for heavy metals by *ICP* and MEM elution cytotoxicity may be applicable on drug product vehicle or process intermediates.

evaluation of product-contact surfaces, test methods for product-contacting materials, typical performance acceptance criteria, a guide to developing specifications for final raw material purchases, and key components of a materials evaluation program.

### Scientific Rationale

Specific premises that support our approach to evaluating extractables from product-contacting surfaces are:

- The use of a *model solvent*, such as water, for extracting material from a product-contact surface is justified as long as the nonsolvent ingredients are shown to be nonextracting or exist in low concentrations.
- The surface-to-volume ratios of the extraction procedure that are used are significantly higher than any experienced in production. Our extraction ratios are comparable to those specified in *USP* 25 (see the "Examples of Test Protocols" box) for various extraction procedures (3).
- The toxicology tests employed meet or exceed USP Class VI or *minimum essential medium (MEM)* elution cytotoxicity requirements (4,5).
- The toxicological impact of any extractables can be evaluated by considering the toxicity of the extractables, the concentration of the extractables in the final product, and the maximum API daily dose.

### Evaluating Product-Contact Surfaces

To develop a system for evaluating product-contact surfaces, you must have a thorough knowledge of the process stream. To make a thorough evaluation, you need to know:

- the materials of construction
- the process solutions or solvents
- the duration of product contact with various surfaces
- the product-contact surface areas
- the potential for extractables at various process stages
- other information that can be derived from studying the process stream.

Using the process-stream information, materials can be prioritized to ensure that company resources are directed toward the most critical, *high-risk materials*. The form in the "Relative Risks: Prioritizing Extractables" box can assist you in prioritizing extractables.

**Step-by-step evaluation.** The basic steps of a product-contact extractables evaluation are described in the "Step-by-Step Extractables Evaluation" box.

### Test Methods

*Model solvent extraction* test methods are typical for generating potential extractables from a material and for quantifying and evaluating those extractables. Tests on model solvent extracts may be evaluated against test limits from *compendial sources* when those are available. Model solvents that contain buffers can also be used to generate and evaluate extractables from product-contacting surfaces. Buffers, however, are likely to make accurately determining the levels and types of extractables in the process stream more difficult.

## Step-by-Step Extractable Evaluation

An extractables evaluation of all product-contact surfaces requires a thorough knowledge of the process stream. Using process stream information, a prioritization of contact materials (see the "Relative Risks" box), and the basic steps below, a systematic evaluation program can be developed.

The basic steps of a product-contact extractables evaluation are described below.

**Step 1.** Create a list of all product-contact surface materials in your pharmaceutical production process stream specifying at a minimum the material type (for example, stainless steel, polypropylene, and EPDM), the material manufacturer, and the manufacturer catalog number.

A list of the materials and process combinations that typically receive high priority are also listed in the "Relative Risks" box.

**Step 2.** Prioritize all product-contact surface materials in the manufacturing process by the potential risk that material might cause to the API. This initial assessment should use all data and information available and should include the following parameters.

- proximity to the API
- extraction capability of solvent
- length of contact
- area of product-contact surface
- temperature of material at contact
- inherent resistance of the material to extraction
- degree of toxicity of the extractable

**Step 3.** Based on the prioritized list of materials and available company resources, determine the materials on which to begin an extractables evaluation.

**Step 4.** Obtain data on the material extractables. The data can be obtained by internal testing or adequate data may be available from the vendor. A *materials safety evaluation group* (or the equivalent) within the company can determine what qualification tests need to be performed on the material, its extracts, the model solvent used, and the acceptance criteria for the testing. If adequate data for materials qualification testing (such as USP Class VI or MEM elution cytotoxicity and physicochemical testing) are available from the vendor, internal testing may not be necessary. To ensure that materials are not installed into plant systems inappropriately, initial tests on the materials can be designed for worst-case situations; that is, exposing the material to extreme conditions beyond those that might be used in any part of the entire process stream. (See the "Test Protocols" and "Acceptance Criteria" boxes.)

**Step 5.** Write a purchase specification for each product-contact surface material, keeping in mind that a prior evaluation may have been performed only for a specific use of the material (as identified in Step 1). If a material has already been evaluated for a specific use, and there is a request to use this material in a different part of the process stream, a reevaluation of the material for the new use may be necessary.

In addition to a purchase specification, it can be helpful to generate an *incoming inspection document* with lot-to-lot release requirements.

Test protocols for plastics and elastomers using aqueous-based systems are listed in the "Examples of Test Protocols" box. Although detailed identification and characterization of the chemical composition of *extract* residues is beyond the scope of this article, we highly recommend such characterization when evaluating extracts from high-risk product-contact materials. High-performance liquid chromatography (HPLC), mass spectrometry, and infrared spectrum analysis can be effective in those investigations.

### Typical Acceptance Criteria

Suggested limits for extractables are shown in the "Typical Acceptance Criteria" box along with supporting data for those limits collected over more than 25 years. These performance acceptance criteria correspond to levels of extractables considered acceptable for pharmaceutical product-contact materials.

The suggested criteria reflect reasonable and achievable extractable levels for state-of-the-art materials. Although the criteria are more rigorous than compendial limits, they represent what modern product-contact materials can consistently meet. They are suggested performance acceptance criteria — not required specifications — and some tests may not be applicable (for instance if the product-contact material is being used in a different or unusual way). Companies must determine the acceptability of extractable levels based on the material's specific use within their processes.

The "Materials Expected to Meet or to Fail" box lists materials that can be expected to meet or to fail the suggested criteria when extracted in purified water at 3,000 $cm^2$/L at 70 °C for 24 hours. Many plastics and elastomers used for pharmaceutical product-contact surfaces contain fillers. A list of plasticizers, fillers, stabilizers, and curing agents that are normally acceptable or not acceptable (that is, they yield compounds that either meet or do not meet the acceptance criteria) are also listed in the box.

### Developing Purchase Specifications

Final raw material purchase specifications should be written based on the results of the extractables testing and manufacturer-supplied specifications for each material. For product-contact materials, the purchase specification should contain the following:

- Name of the material
- Grade of material
- Name of the manufacturer
- Name of the supplier (optional)
- Manufacturer's catalog number
- Location of the manufacturer's plant (if you control shipments by facility)
- Chemical test requirements, if any
- Biological test requirements, if any
- Functional test requirements, if any
- Packaging requirements, if any
- Shipping requirements
- Signature of purchase specification author and QA approver
- Specification revision number and date.

Sometimes it may be appropriate to generate one specification that covers many sizes of the same material, such as gaskets and o-rings. Materials with a "lower risk" prioritization may, upon receipt, require only an incoming inspection document to ensure that the correct material has been delivered — with no additional testing required.

## Relative Risks: Prioritizing Extractables

Assessing the relative risk of various pharmaceutical product-contact materials is an important part of an extractables evaluation program. The following table is intended for use as a worksheet by the reader. A single worksheet should be filled out for each product-contacting material.

For the purpose of risk evaluation, we have assigned a risk value to various risk parameters (lowest risk = 1, highest risk = 10). You can use the "Risk of Material in Question" column to insert the relative numerical risk (from the "Risk Values" column) for materials used in your production process.

For example, if the "Proximity to API" is "Final Formulation," you would insert a 10 in the "Risk of Material in question" column.

All the numerical risks for each category are added together at the bottom to get the "Total Risk (Sum)." When all the materials in a system are evaluated, the "Total Risk (Sum)" for each material will enable you to prioritize your risks. The highest "Total Risk (Sum)" material should become the first to be evaluated.

An example of highest risk would be a large sulfur-cured EPDM valve diaphragm pumping final formulation in organic solvent held for extended time at high temperature. An example of lowest risk would be a small bore stainless steel pipe transferring cold water for injection (WFI) at a high flow rate.

**Relative Risk Evaluation Worksheet for Product-Contacting Pharmaceutical Production Materials**

**Material Name:** _____ **ID:** _____

| Risk Variables | Qualifier | Risk Values | Risk of Material in Question |
|---|---|---|---|
| **Proximity to API** | | | |
| Final formulation | | 10 | |
| Purification | | 6 | |
| Fermentation | | 2 | |
| **Extraction Capability of Solvent** | | | |
| High | organic[a] | 10 | |
| Medium | water/organic | ratio | |
| Low | water | 4 | |
| **Length of Contact** | | | |
| High | >30 days | 10 | |
| Medium | >24 hours to 30 days | 6 | |
| Low | <24 hours | 2 | |
| **Product Contact Surface Area** | | | |
| High | >6,000 $cm^2$ | 10 | |
| Medium | 500 to 6,000 $cm^2$ | 6 | |
| Low | 5 to 500 $cm^2$ | 2 | |
| **Cytotoxicity of Extractables** | | | |
| High | 100% cell death | 10 | |
| Medium | 50% cell death | 4 | |
| Low | 0% cell death | 0 | |
| **Temperature** | | | |
| High | >70 °C | 10 | |
| Medium | 37 °C to 70 °C | 6 | |
| Low | 2 °C to 37 °C | 2 | |
| **Inherent Material Resistance to Extraction** | | | |
| High | elastomer/plasticized polymers | 10 | |
| Medium | rigid plastic and Type II and III glass | 4 | |
| Low | metals and Type I glass | 1 | |
| **Total Risk (Sum)** | | | |

[a]Surfactant materials may lead to higher extractables than organic solvents.

## Potential High-Priority Material Combinations to Assess

The following equipment or parts often used in combination with potential high-priority materials should be assessed for extractables:

- bags and containers for fermentation media
- bags and containers for purification buffers
- bags for holding frozen, ultrafiltered product
- chromatography resins (can be quite critical if not well understood and evaluated; residue, ligand leaching, and creation of fines are among the considerations)
- elastomeric purification transfer hoses
- EPDM or silicone valve diaphragms
- EPDM valve diaphragms on final purification skid
- final filter
- gaskets on final bulk tank
- hoses on final chromatography skid
- O-rings in final bulk tank
- other elastomers on final chromatography skid
- pumps on final chromatography skid
- silicone boot on filling machine
- silicone tubing to filling machine
- ultrafilter and diafilter units

## Typical Acceptance Criteria

The following tables provide typical acceptance criteria for product-contact materials and their aqueous extracts. The suggested purified water extract acceptance criteria are based on 25 years of data collected at 3,000 $cm^2$/L, 70 °C, 24 hours, which was the USP surface-to-volume ratio at the time the studies were initiated.

Recently, the USP surface-to-volume ratio for plastics has been set at 6,000 $cm^2$/L. Evaluation programs should use the ratio from the current USP. The criteria specified in the following tables are more rigorous than those from compendial sources but represent what modern product-contact materials can consistently meet. For comparison, various compendial tests and limits are shown. The data that support the typical acceptance criteria are listed in the next table.

## Typical Extractables Acceptance Criteria

**Acceptance Criteria for Extracts[a]**

| Tests on Extracts | Typical Acceptance Criteria |
|---|---|
| pH | 3.5–9.0 |
| Conductivity | <40 ppm as NaCl |
| Nonvolatile residue | <50 mg/L |
| Total organic carbon | <50,000 ppb |
| Oxidizable substances | <3.0 mEq $KMnO_4$/L |
| Heavy metals[b] | <1 ppm as lead |

[a]These criteria are based on industry experience.
[b]Defined by USP

**Acceptance Criteria for Solids[a]**

| Tests on Solids | Typical Acceptance Criteria |
|---|---|
| Heavy metals[b] by ROI-ICP | No single heavy metal >10 ppm<br>Total heavy metals <50 ppm |
| Identity by IR | Equivalent to reference |

[a]These criteria are based on industry experience.
[b]Defined by USP

## Comparison Compendial Tests and Limits from the Pharmacopoeias of the United States, Europe, and Japan

**Compendial Criteria for Plastics (USP) (3)**

| Tests Method[a] | Limit |
|---|---|
| Physicochemical nonvolatile residue (NVR) on purified water extract (mg/L) | <300 |
| Residue on ignition of NVR (mg) | <5 |
| Heavy metals on extract (ppm) | <1 |
| Buffer capacity on extract | <10.0 mL of 0.010 N acid or base vs. blank |
| Class VI (mouse, rabbit, implant) | Pass |
| MEM elution cytotoxicity | Pass |
| Microbial load (CFU/g of CFU/mL) | <300 |
| Bacterial endotoxin | USP limit |

[a]Extraction conditions: 3,000 $cm^2$/L, 70 °C, 24 hours

**Compendial Criteria for Plastics (EP) (7)**

| Tests Method[a] | Limit |
|---|---|
| Appearance on extract | Clear, colorless |
| Absorbance from 230 nm to 360 nm | <0.20 |
| Reducing substances | <1.5 mL 0.002 M $KMnO_4$ vs. blank |
| Transparency | Pass |

[a]Extraction conditions: 500 $cm^2$/L, 121 °C, one hour

**Compendial Criteria for Plastics (JP) (9)**

| Tests Method | Limit |
|---|---|
| **Extractable Substances (3,000 $cm^2$/L, 70 °C, 24 hours)** | |
| Residue on ignition | Report |
| Heavy Metals | Report |
| Lead | Report |
| Cadmium | Report |
| Tin | Report |
| **Extractable Substances (6,000 $cm^2$/L, 70 °C, 24 hours)** | |
| Foaming Test | Time to foam break |
| pH | Report vs. control |
| $KMnO_4$ reducing substances | Report mL 0.002 M $KMnO_4$ vs. blank |
| UV absorption | Report maximum absorbance between 220–240 nm and between 241–350 nm |
| Residue on evaporation | Report |
| Fine particles | Report particles of 5–10 μm, 20–25 μm, and >0.25 μm/mL |
| Cytotoxicity test | Pass |
| Functional tests (transparency, water vapor permeability, leakage) | Report |

## *Data Supporting the Acceptance Criteria in the "Typical Acceptance Criteria" Box*

| Category[a] | pH | Conductivity (ppm as NaCl) | Oxidizable Substances (mEq $KMnO_4$/L)[b] | Nonvolatile Residue (mg/L) | TOC (ppb)[b] | Cytotoxicity | |
|---|---|---|---|---|---|---|---|
| | | | | | | Distilled Water[b,c,d,e] | Plasmanate[b,c,d,e] |
| Acrylonitrile-butadiene-styrene | 7.52 | 4.0 | 0.12 | 0.0 | N/A | 0 | 0 |
| Acrylonitrile-butadiene-styrene | 5.95 | 0.2 | 0.25 | 1.6 | N/A | 0 | 0 |
| Acrylonitrile-butadiene-styrene, white | 6.66 | 1.2 | <0.2 | 1.7 | N/A | 0 | N/A |
| Acrylonitrile-butadiene-styrene, white | 7.80 | 8.5 | 0.92 | 2.0 | N/A | 0 | N/A |
| Acrylonitrile, clear | 5.80 | 2.0 | 0.05 | 0.0 | N/A | (±) | (±) |
| Cellulose esters, filter membrane (4,600 $cm^2$)[f] | 4.95 | 15.0 | <0.1 | 121.1 | N/A | 0 | 0[g] |
| Cellulose propionate | 4.28 | 20.0 | 1.67 | 0.8 | N/A | 0 | 0 |
| EPDM | 7.60 | 24.0 | N/A | 62.0 | 86,990 | 4+ | 4+ |
| EPDM (no postcure) | 7.05 | 20.0 | 81.1 | 34.0 | N/A | 0 | 0 |
| EPDM (nonpost cured) | 6.91 | 2.0 | 18.97 | 19.0 | N/A | N/A | N/A |
| EPDM (postcured 16 hr at 135 °C) | 7.00 | 20.0 | 10.2 | 74.0 | N/A | 0 | 0 |
| EPDM (postcured 16 hr at 275 °F) | 6.90 | 10.0 | 1.38 | 22.0 | N/A | 0 | 0 |
| EPDM (postcured 2 hr at 300 °F) | 7.00 | 16.0 | 1.6 | 22.0 | N/A | 0 | 0 |
| EPDM (postcured 72 hr at 260 °F) | 6.81 | 2.0 | 0.444 | 11.6 | N/A | N/A | N/A |
| EPDM (postcured 72 hr at 260 °F) | 6.90 | 10.0 | 1.38 | 22.0 | N/A | 0 | 0 |
| EPDM, black (food grade) | 9.40 | 249.0 | N/A | 460.0 | 157,000 | N/A | N/A |
| EPDM, black (no postcure) | 7.72 | 40.0 | 28.4 | 146.0 | N/A | 0 | 0 |
| EPDM, black (postcured 2 hr at 150 °C) | 6.92 | 40.0 | 19 | 74.0 | N/A | 0 | 0 |
| EPDM, gray | 10.40 | 155.0 | N/A | 284.0 | 224,000 | N/A | N/A |
| EVA, 12%, film | 4.68 | 4.7 | 0.02 | 1.6 | N/A | 0 | 0 |
| Neoprene | 8.08 | 752.0 | N/A | 1,053.0 | 315,900 | 4+ | 3+ |
| Neoprene | 6.93 | 42.0 | N/A | 975.0 | 59,500 | 4+ | 4+ |
| Nitrile | 7.54 | 22.6 | N/A | 38.0 | 13,269 | 0 | 3+ |
| Nylon 6,6, filter membrane (4,600 $cm^2$)[f] | 4.32 | 9.8 | 0.61 | 24.0 | N/A | 0 | 0[h] |
| Polyacetal | 4.48 | 22.3 | N/A | 6.0 | 28,000 | N/A | N/A |
| Polyacetal | 4.63 | 17.8 | N/A | 5.0 | 44,400 | N/A | N/A |
| Polyamide, OH mod., filter membrane (4,600 $cm^2$)[f] | 4.95 | 3.0 | 0.23 | 4.0 | N/A | 0 | 0 |
| Polycarbonate | 5.95 | 0.02 | 0.07 | 0.0 | N/A | 0 | 0 |
| Polyetheretherketone, glass-filled | 7.00 | 2.10 | N/A | 2.0 | 1,033 | 0 | 0 |
| Polyetheretherketone, glass-filled | 5.80 | 0.50 | N/A | 1.0 | 760 | 0 | 0 |
| Polyethersulfone, filter membrane (4,600 $cm^2$)[f] | 4.98 | 5.89 | 8 | 51.4 | N/A | 0 | 4+ |
| Polyethylene | 6.15 | 0.05 | 0.009 | 0.0 | N/A | 0 | 0 |
| Polyethylene, film | 6.22 | 0.8 | N/A | 19.2 | 16,600 | 0 | 0 |
| Polyethylene, film | 6.00 | 0.7 | N/A | 0.4 | 9,200 | 0 | 0 |
| Polyethylene, natural | 5.97 | 1.5 | N/A | 9.0 | 1,405 | 0 | 0 |
| Polyethylene, Tyvek | 6.30 | 1.1 | N/A | 2.0 | 14,500 | 0 | 0 |
| Polypropylene, felt bag | 5.30 | 0.60 | N/A | 23.0 | 11,710 | 0 | 0 |
| Polypropylene, filter membrane (6,040 $cm^2$)[f] | 6.10 | 0.15 | 0.03 | 1.2 | N/A | 0 | 0 |
| Polypropylene, natural | 5.43 | 1.10 | N/A | 4.0 | 1,655 | 0 | 0 |
| Polypropylene, tan | 6.30 | 0.2 | 0.003 | 0.0 | N/A | 0 | 0 |
| Polyvinylchloride | 5.50 | 53.00 | N/A | 455.0 | 180,200 | 0 | 4+ |
| Polyvinylchloride, DEHP | 5.00 | 2.0 | 1.67 | 6.8 | N/A | 0 | 0 |
| Polyvinylchloride, TOTM | 5.70 | 0.7 | 0.24 | 2.8 | N/A | 0 | 0 |
| Polyvinylidenefluoride | 5.80 | 0.7 | N/A | 0.0 | 847 | 0 | 0 |
| Polyvinylidenefluoride | 4.60 | 5.7 | N/A | 1.0 | 2,507 | 0 | 0 |

*Continued on page 32*

[a]Extractions were run in purified water at 3,000 $cm^2$/L, 70 °C, for 24 hours or in human serum albumin, 3,000 $cm^2$/L, 50 °C for seven days.
[b]N/A= test not run [c]0 = no cells destroyed or damaged [d]4+ =100% of cells destroyed or damaged [e](±) = less than 25% of cells destroyed or damaged
[f]Filter membranes were evaluated by rinsing a 10-in cartridge with 180 L of WFI and then extracting the cartridges statically at 70 °C for 24 hours.
[g]at 1,630 $cm^2$ [h]at 2,400 $cm^2$

## Materials Expected to Meet or to Fail Acceptance Criteria

**Materials Expected to MEET** the listed acceptance criteria when extracted at 3,000 $cm^2$/L, at 70 °C, for 24 hours in purified water.

Fluorinated ethylene propylene (FEP)

Perfluoroalkoxy resin (PFA)

Peroxide cured, postcured EPDM

Platinum cured silicone

Polycarbonate

Polyester

Polyethylene

Polymethylpentene (TPX)

Polypropylene

Polysulfone

Polytetrafluoroethylene (Teflon)

Polyvinylidene difluoride (Kynar)

Resin cured halo-butyl elastomers

Stainless steel (302, 304, 312, 316, and 316 L)

Viton, carbon black filled

**Materials Expected to FAIL** the listed acceptance criteria when extracted at 3,000 $cm^2$/L, at 70 °C, for 24 hours in purified water.

Amorphous nylon (other than filter membranes)

Neoprene

Peroxide cured, nonpost cured EPDM

PVC plasticized with DEHP

Rigid PVC with organotin stabilizers

Sulfur-cured elastomers of all types including natural rubber, Buna N (nitrile), EPDM, and styrene-butadiene

Viton, lead oxide filled

**Plasticizers, Fillers, Stabilizers, and Curing Agents Expected to MEET** acceptance criteria when compounded (based on 3,000 $cm^2$/L in purified water, at 70 °C for 24 hours and on HSA at 50 °C for seven days).

Carbon black

Silica

Titanium dioxide

Ultramarine blue

Zinc oxide

**Plasticizers, Fillers, Stabilizers, and Curing Agents Expected to FAIL** acceptance criteria when compounded or to be carcinogenic when compounded (based on 3,000 $cm^2$/L in purified water, at 70 °C for 24 hours and on HSA at 50 °C for seven days).

Barium stabilizers

Benzidine based dyes

Cadmium stabilizers

Clay (aluminum silicate base)

Dicumyl peroxide (unless properly post cured)

Diethylhexyl phthalate

Heavy metal based dyes

Lead oxide (filler or component of leaded glass)

Mercaptobenzothiazole (and thiazoles generally)

Organotin compounds

*Supporting Data continued from page 30*

## *Data Supporting the Acceptance Criteria in the "Typical Acceptance Criteria" Box (continued)*

| Category[a] | pH | Conductivity (ppm as NaCl) | Oxidizable Substances (mEq $KMnO_4$/L)[b] | Nonvolatile Residue (mg/L) | TOC (ppb)[b] | Cytotoxicity: Distilled Water[b,c,d] | Cytotoxicity: Plasmanate[b,c,d,e] |
|---|---|---|---|---|---|---|---|
| PVC, DEHP | 5.50 | 0.7 | 3.97 | 15.2 | N/A | (±) | 0 |
| PVC–acrylonitrile, filter membrane (6,000 $cm^2$)[f] | 4.71 | 8.0 | 0.74 | 44.8 | N/A | 0 | (±) |
| PVDF, filter membrane (6,000 $cm^2$)[f] | 5.57 | 3.1 | 0.84 | 16.8 | N/A | 0 | 0 |
| Silicone | 3.32 | 90.0 | 1.91 | 89.2 | N/A | 0 | N/A |
| Silicone, clear | 5.15 | 5.0 | 2.2 | 14.8 | N/A | 0 | 0 |
| Silicone, clear | 5.45 | 1.0 | 0.07 | 1.6 | N/A | 0 | 0 |
| Silicone, clear | 4.38 | 4.0 | 0.15 | 0.8 | N/A | 0 | 0 |
| Silicone, clear | 5.72 | 0.2 | 0.2 | 0.4 | N/A | 0 | 0 |
| Silicone, clear, Pt cured | 6.22 | 1.8 | 0.06 | 6.8 | N/A | N/A | 0 |
| Silicone, clear, Pt cured | 5.80 | 0.9 | 0.04 | 0.4 | N/A | 0 | 0 |
| Silicone, red | 5.60 | 5.0 | 1.73 | 12.8 | N/A | 0 | 0 |
| Silicone, red | 8.35 | 10.0 | 4.61 | 67.2 | N/A | 0 | 0 |
| Silicone, red | 10.10 | 45.0 | N/A | 263 | 107,000 | 0 | 0 |
| Silicone, white (postcured 16 hr at 275 °F) | 6.42 | 80.0 | 5.11 | 120.0 | N/A | 0 | (±) |
| Silicone, white (postcured 2 hr at 300 °F) | 7.90 | 200.0 | 4.74 | 326.0 | N/A | 0 | 0 |
| Silicone, white, no postcure | 4.80 | 8.0 | 2.61 | 14.8 | N/A | 0 | 0 |
| Silicone, white, no postcure | 7.80 | 800.0 | 74.2 | 862.0 | N/A | (±) | 0 |
| Silicone, white, no postcure | 5.20 | 2.0 | 1.41 | 1,932.0 | N/A | (±) | 0 |
| Stainless steel, 316, powder, max conc. | 6.75 | 7.0 | 0.17 | 11.6 | N/A | 0 | 0 |
| Styrene-acrylonitrile | 6.30 | 0.2 | 0.07 | 0.0 | N/A | 0 | 0 |
| Styrene-acrylonitrile | 6.45 | 0.1 | 0.0 | 2.0 | N/A | 0 | 0 |
| Teflon, diaphragm | 5.68 | 0.8 | N/A | 0.0 | 574 | 0 | 0 |
| Teflon, strips | 5.38 | 1.8 | N/A | 1.0 | 462 | 0 | 0 |
| Teflon, tape | 5.70 | 0.6 | N/A | 15 | 2,260 | 0 | 0 |
| Viton, black | 9.70 | 100.0 | 0.4 | 30.4 | N/A | 0 | 0 |

[a]Extractions were run in purified water at 3,000 $cm^2$/L, 70 °C, for 24 hours or in human serum albumin, 3,000 $cm^2$/L, 50 °C for seven days.
[b]N/A= test not run [c]0 = no cells destroyed or damaged [d](±) = less than 25% of cells destroyed or damaged [e] 4+ =100% of cells destroyed or damaged
[f]Filter membranes were evaluated by rinsing a 10-in cartridge with 180 L of WFI and then extracting the cartridges statically at 70 °C for 24 hours.
[g]at 1,630 $cm^2$ [h]at 2,400 $cm^2$

Purchase specifications may also be used as guidelines or acceptance criteria for purchasing equivalent materials from new vendors.

**Supplier statements of acceptability.** It is not uncommon for suppliers to state that a material is "FDA Approved," but that statement is never appropriate. FDA does not "approve" materials.

When a supplier states that a material is "FDA Approved," it normally means that the material is compounded from chemicals selected from the lists in 21 CFR 175–178 (6). Materials composed from items on those lists are acceptable for contact with dry or fatty foods. Frequently, composites compounded from materials on those lists do not meet the typical acceptance criteria in this article.

### Key Components in the Program

Good programs for evaluating extractables require management support, detailed and understandable policies for accomplishing the evaluations, and appropriate raw material specifications for purchases.

Resource documents that can help you in setting up an extractables evaluation program are listed in the "Resources and Suggested Reading" box.

**Commitment from upper management** is critical before implementing a materials evaluation program. Garnering that commitment can be supported by referring to FDA and ICH regulations (such as 21 CFR 211.65 and ICH API GMPs 5.11) (1,2). It is also critical that all involved groups — quality assurance, quality control, engineering, process development, and purchasing, for instance — understand the importance of the evaluation program, because they will need to implement and maintain the program. Commitment from the quality assurance unit is essential because that unit should have oversight of the materials evaluation program and its associated controls.

**Procedural controls.** A standard operating procedure (SOP) or similar document should be written specifying how your company will choose and purchase product-contacting materials and detailing which materials will or will not be tested for extractables. That document can include how the material will be ordered, received, stored, tested, and placed into service. The SOP should also include the function responsible for fulfilling each aspect of the materials evaluation program.

## Resources and Suggested Reading


### ASTM References

(ASTM International, West Conshohocken, PA, www.astm.org).

ASTM F-619: Standard Practice for Extraction of Medical Plastics.

ASTM F-719: Standard Practice for Testing Biomaterials in Rabbits for Primary Skin Irritation.

ASTM F-748–87: Practice for Selecting Generic Biological Test Methods for Materials and Devices.

ASTM F-749: Standard Practice for Evaluating Material Extracts by Intracutaneous Injection in the Rabbit.

ASTM F-750-87: Practice for Evaluating Material Extracts by Systemic Injection in the Mouse.

ASTM F-756: Standard Practice for Assessment of the Hemolytic Properties of Materials.

ASTM F-813-83(1988): Practice for Direct Contact Cell Culture Evaluation of Materials for Medical Devices.

ASTM F-895-84: Test Method for Agar Diffusion Cell Culture Screening for Cytotoxicity.

ASTM E-2097-00: Standard Guide for Determining the Impact of Extractables from Nonmetallic Materials on the Safety of Biotechnology Products.

### ISO References

(International Organization for Standardization, Geneva, www.iso.ch).

ISO 10993-1: Biological Evaluation of Medical Devices, Part 1: Guidance on Selection of Tests.

ISO 10993-5: Biological Evaluation of Medical Devices, Part 5: Tests for In Vitro Cytotoxicity.

ISO 10993-5: Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Sensitization.

ISO 10993-5: Biological Evaluation of Medical Devices, Part 11: Tests for Systemic Toxicity.

### USP References

(U.S. Pharmacopeial Convention, Inc., Rockville, MD, www.usp.org).

USP Subcommittee on In Vitro Toxicity, "Stimuli to the Revision Process," *Pharmacopeial Forum* (January–February 1989), pp. 4804–4811.

USP, "Stimuli to the Revision Process, Container/Closure Standard Requirements in Four Major Pharmacopoeias (USP, EP, BP, JP); A Comparative Review, *Pharmacopeial Forum* (July–August 1992), pp. 3772–3775.

USP, "Elastomeric Closures for Injection," Ch. <381> *USP 25–NF20, Supplement 1*, (2002).

### Regulations, Guidances, and Industry Associations

"Drug Product Containers and Closures," *Code of Federal Regulations, Food and Drug*, Title 21, Part 211.94 (U.S. Printing Office, Washington, DC).

EP, *Rubber Closures for Containers for Aqueous Parenteral Preparations, for Powders and for Freeze-Dried Powders*, 3.2.9 (European Pharmacopoeia, Strasbourg, France. 4 February 2002, www.pheur.org).

ICH, *Guidance for Industry, Q7A: Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (International Committee on Harmonisation, Geneva).

PDA Research Committee, "Generic Test Procedures for Elastomeric Closures," *Technical Information Bulletin No. 2* (Parenteral Drug Association, Bethesda, MD, April 1979).

PDA, "Extractables from Elastomeric Closures: Analytical Procedures for Functional Group Characterization and Identification," *Technical Methods Bulletin No. 1*, (Parenteral Drug Association, Bethesda, MD, 1980).

### Magazine and Book References

Begley, T. and Hollifield, H.C., "Liquid Chromatographic Determination of Residual Reactants and Reaction By-Products in Polyethylene Terephthalate," *JAOAC* 72, 468–470 (1989).

Cruz, L.A. et al., "Influence of Solute Degradation on the Accumulation of Solutes Migrating into Solution from Polymeric Containers," *Pharm. Res.* 7, 967–972 (1990).

Del Tito, Jr., B.J., Tremblay, M.A., and Shadle, P.J., "Qualification of Raw Materials for Clinical Biopharmaceutical Manufacturing," *BioPharm* 9(10), 45–49 (November, 1996).

Duffus, J.H., "Heavy Metals: A Meaningless Term," *Chem. Int.* 23(6), November 2001).

Grave, E., "Material Selection for Components in a Pilot Plant Fermentation System," *BioPharm* 1(1), 22–28 (January 1988).

Guaita, C., "HPLC Analysis of Cyclo-Oligoamides 6 and 66," *Makromol. Chem.* 185, 459–465 (1984).

Jenke, D.R., "Additive Model for the Evaluation of Interactions Between Aqueous Solutes and Multicomponent Container Materials," *J. Paren. Sci. Technol.* 45, 233–238 (1991).

Jencke, D.R. et al., "Accumulation Model for Solutes Leaching from Polymeric Containers," *J. Paren. Sci. Technol.* 47, 172–176 (1993).

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Northrup, S.J., "Cytotoxicity Tests of Plastics and Elastomers: Stimuli to the Revision Process," *Pharmacopeial Forum*, p. 2939 (September–October 1984).

"Pharmaceutical and Biotechnology Quality Control," *The Gold Sheet* 36(1), 1–10 (2002).

"Quality Assurance of Production Materials for Biotechnology," *Quality Assurance for Biopharmaceuticals*, J.F. Huxsoll, Ed. (J. Wiley & Sons, Inc., New York, 1994).

Reif, O.W., Solkner, P., and Rupp, J., "Analysis and Evaluation of Filter Cartridge Extractables for Validation in Pharmaceutical Downstream Processing," *J. Pharm. Sci. Technol.* 50(6), 399–410 (1996).

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Stone, T.E. et al., "The Model Stream Approach: Defining the Worst-Case Conditions," *Pharm. Technol.* 20(2), 34–51 (1996).

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Victor, R., Chan, A.K., and Mattoon, M., "Aluminum Contamination in Albumin Solutions from Glass Storage," *Transfusion* 28(3), 290 (1990).

Weitzmann, C., "The Use of Model Solvents for Evaluating Extractables from Filters Used to Process Pharmaceutical Products," *Pharm. Technol.* 21(4), 72–99 (April 1997).

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### Company References

"Guide to Extractables in Effluents from Pall P-Rated Ultipor N66 and N66 Posidyne Filter Cartridges" (Pall Ultrafine Filtration Company, East Hills, NY, 1995, www.pall.com).

Katz, H., "Extractables in Pharmaceutical Grade Filter Elements," (Pall Ultrafine Filtration Company, East Hills, NY, 1981, www.pall.com).

"Validation Guide for Pall 0.2-µm Ultipor N66 and N66 Posidyne Membrane Cartridges" (Pall Ultrafine Filtration Company, East Hills, NY, 1980, www.pall.com).


Other useful procedures or documents to be generated and maintained include a description of how to generate purchase specifications and incoming materials inspection documents, lists of approved product-contacting materials with the associated approved vendors and applications, and a material-receiving procedure. Change control procedures should be in place to ensure the currently approved materials and their associated approved uses are not changed without prior assessment and approval by quality assurance.

**Administrative controls.** In addition to the procedural controls, other controls are needed to ensure that the materials evaluation program is effective. Suggested administrative controls include written purchase specifications for product-contact material, written and approved test methods for product-contact materials, a vendor evaluation program, and a data management and recovery system.

A controlled area for storing and dispensing released product-contact materials should be maintained to ensure

that maintenance or facility personnel use only released materials for production equipment that will contact a product. All released materials should be adequately labeled to ensure that they are easily recognized as approved product-contacting materials. Administrative controls should also ensure that facility personnel know which approved material to use in specific product-contact equipment.

### When to Test

Before phase 1 clinical trials, a complete list of product-contact materials should be assembled and an initial assessment performed for high-risk materials. Manufacturer reference information should be assembled on all product-contact materials, and testing should be completed on identified high-risk materials.

Before phase 3 clinical trials, a complete packet on each product-contact material should be finalized, with applicable testing results and designated use approved by quality assurance.

### Successful Extractable Assessments

Evaluation of potential extractables from product-contact surfaces is an area of increasing interest in the manufacture of biopharmaceuticals. Achieving a successful assessment of extractables requires thorough knowledge of the process equipment, construction materials, process stream, and potential extractables encountered during the production of the biopharmaceuticals.

Understanding the risks to the product when it is exposed to potential extractables during various phases of the process stream aids in prioritizing the evaluation of each product-contact material. Regulatory and compendial requirements can help when designing studies of extractables and when developing optimal assays and evaluation methods to ensure efficient use of resources.

Management needs to understand that the program will require ongoing resources throughout the development and production phases. Establishing a materials evaluation program early in the development of a drug product can give assurance that extractables from product-contact surfaces do not alter the safety or purity of the biopharmaceutical. ***BPI***

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(1) "Equipment Construction," *Code of Federal Regulations, Food and Drugs* Title 21, Part 211.65 (U.S. Government Printing Office, Washington, DC, revised 1 April 2002).

(2) "Good Manufacturing Practice Guide for Active Pharmaceuticals: Process Equipment, Design and Construction," ICH Q7A: CPMP/ICH/1935/00, ICH API 5.11 (International Conferences on Harmonisation, Geneva), published in *Federal Register* 66(186), 25 September 2001, pp. 49028–49029.

(3) "Physicochemical Tests, Plastics: Containers," Ch. <661>, *USP 25–NF 20, Supplement 1* (2002).

(4) "Biological Reactivity Tests, In Vitro," Ch. <87>, *USP 25–NF 20*, Supplement 1 (2002).

(5) "Biological Reactivity Tests, In Vivo," Ch. <88>, *USP 25–NF 20, Supplement 1* (2002).

(6) *Code of Federal Regulations, Food and Drugs* Title 21, Parts 170–199 (U.S. Government Printing Office, Washington, DC).

(7) EP, "Plastic Containers for Aqueous Solutions for Parenteral Infusion," 3.2.2.1 (4 February 2002).

(8) JP, "Test Methods for Plastic Containers," 61, XIV (2001).