Materials of Construction for Biopharmaceutical Water Systems, Part 2

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Stainless Steel

Selection of Stainless Steels

Stainless steels are uniquely qualified for bioprocessing applications not only because of their long service life, availability, and fabricability, but also because they are non-corroding, non-contaminant, can be polished to very smooth finishes, are strong and rigid, can withstand heat and chemical sterilization treatments, and are easily welded. With more than 70 standard types of stainless steel produced, the industry's workhorse is the austenitic group which includes types 304 and 316 and their L or low carbon content variations. With concerns for higher corrosion resistance, the low carbon superaustenitic stainless steel AL-6XN (6% Molybdenum) and the Nickel-based alloys, Hastelloy C (C-22, C-276), are becoming notoriously important in the fabrication of vessels, piping, tubing, and fittings (see Table 1). Finally, the cast stainless alloys such as CF- 8 (similar to 304), CF-8M (similar to 316), and CF-3M (similar to 316L) utilized in pumps, various types of valves, (particularly ball type), and fittings occupy a prominent position in the industry.

Standards and Codes

In some biopharmaceutical industry circles, there is the belief that the stringent specifications that rule biopharmaceutical processes have no comparison with the food and dairy industries. Actually, almost the reverse is true; the present standards and specifications for tubing fabrication and their product/solution contact surfaces, as well as the installation of systems, have their origin in the dairy industry through the 3-A Sanitary Standards and Accepted Practices, now known as 3-A Sanitary Standards, Inc. (3-A SSI). Published by the International Association for Food Protection (IAFP) and the Milk Industry Foundation (MIF), these standards dealt first with the sanitary aspects of polished metal tubing used to conduct dairy products in processing lines or systems that also included sanitary fittings, and secondly, with the cleaning of rigid solution lines and the clean-in- place (CIP) units used to circulate the pre-rinse, rinse, cleaning solutions, and post-rinse liquids used for cleaning and sanitizing the product pipelines and process equipment.

As the pharmaceutical industry advanced, the development of new technologies to make or modify products by microbial and biochemical processes using living organisms or substances from those organisms (Biotechnology) increased the need for more stringent regulations. Many of these regulations are related to systems cleanability and sterility, standardization of manufacturing methods, and integration of fabrication standards covering vessels, components, and equipment. The American Association of Mechanical Engineers (ASME), through its Council on Codes and Standards (CSS) and a directive to the Board on Pressure Technology Codes and Standards (BPTCS), initiated the creation of what is now known as the Bioprocessing Equipment (BPE) [6]. This Standard directly (or by reference) covers requirements for materials, design, fabrications, examinations, inspections, testing, certifications (for pressure systems), and pressure relief (for pressure systems) of vessels and piping for bioprocessing systems. Requirements of this Standard apply to all parts that contact the product, raw materials, or product intermediates during manufacturing, development, or scale-up, and all equipment or systems that are a critical part of product manufacturing, such as WFI, clean/pure steam, ultrafiltration, and intermediate product storage. While the ASME BPE Standard addresses requirements applicable to the design of equipment and components, other codes and standards define specific requirements for the manufacturing of components critical to the processes and support utilities, particularly piping, tubing, and fittings [10].

Product and/or Solution Contact Surface Finishes

Surface finishes, accessible and inaccessible, that directly or indirectly come in contact with a designated product/solution stream in bioprocessing equipment and distribution system components, must exhibit specific surface roughness characteristics to enhance their cleaning and sterilization. It has become absolutely necessary to have a universally recognized and accepted surface roughness measurement standard for these surfaces, and the **R**a value has been chosen to describe this criterion. This standard value, known as Arithmetic Average Roughness, is defined as, "*the arithmetic average height of roughness component irregularities from the mean line measured within the sample length (L)*" [11]. The derivation **R**a is usually expressed in microinches (µin), and/or micrometers (µm or micron), and it is measured with profilometers and/or borescopes. (1 µin = 0.0254 µm or micron, and 1 µm = 39.375 µin).

Electropolished (EP) Finishes

Because some processes in the pharmaceutical industry require smoother product/solution contact surfaces to achieve a purer product with less danger of bacteria growing in surface defects or cross-contamination of one product with another [1], in addition to purely mechanical finishes, sanitary equipment, tubing, and components are also available in highly polished surfaces.

These highly polished surfaces are achieved by electropolishing, also known as “chemical machining” and/or “reverse plating”, an electrochemical process far superior to any available mechanical process for the removal of surface imperfections in stainless steels [4]. Electropolishing levels and brightens the material surface by anodic dissolution in flowing mixed acid solutions, sometimes with organic additives, (electrolyte) and a cathode that is pulled through the inside of the tube or component (anode). When the proper combination of electrolyte current temperature is attained, the high points of surface irregularities (or high current density areas) are selectively removed at a greater rate than the remainder of the surface resulting in improved surface measurements.

In addition to appearance, electropolished products offer other advantages such as reduction of debris adherence, an increased chromiumto- iron ratio, which improves corrosion resistance, the creation of a passive layer that is free from iron contamination, improved ability to visually detect surface defects, and improved mechanical property performance through the minimization of stress risers. It must be noted that individual components can be electropolished, but not whole systems that may include equipment, piping, and other components (See Stainless Steel Passivation).

Joining Techniques

Requirements for the joining of bioprocessing equipment including vessels and tanks (built to ASME Boiler and Pressure Vessel Code (BPVC), Section VIII, Division 1), heat exchangers, pumps, piping, tubing, and fittings, are described in Part MJ of the ASME BPE and are limited to process systems that contact bioprocessing products or product/solution streams. Welding procedures for pressure vessels, tanks, piping, and hygienic tubing systems shall be qualified in accordance with ASME BPVC, Section IX.

Because tubing systems occupy a most conspicuous place in the construction of bioprocessing facilities, special emphasis has been placed upon the prevalent method for joining these systems. Connections between tube and tube or tube and fitting, and even tube/fitting to equipment, can be accomplished by diverse means. However, the use of mechanical joints where impurities entrainment may occur, such as flanges, threaded joints, or even hygienic clamp type joints must be kept to a minimum. Thus, systems shall preferentially be joined using square butt-welding practices only because they present the lowest risk of contamination.

Automatic Orbital Welding - Typically, square butt-welded tubing joints are made using automatic orbital welding equipment which fuses the thin wall tubes and fittings together in a totally inert environment without the use of filler materials (autogenous weld) [2]. Essentially, an arc established between a tungsten electrode (installed in a rotor within the weld head) and the tubing, accomplishes the fusion weld. This process consists of a series of spot welds in which the main welding current penetrates the material and the background current chills the puddle. The quality of the fusion joint that is made by this equipment is predicated on the use of two pieces of material of the same thickness and grade or type; therefore, great care must be exercised in material and component selection.

The actual welding process requires the tube/tube or tube/fitting to be placed in a welding head provided with clamping jaws to securely hold the parts in position and in alignment with the tungsten electrode contained within the head. The entire area to be welded is then enclosed in the welding head, forming a chamber that is filled with shielding gas, usually argon, to prevent oxidation of the welded material during the weld sequence. Meanwhile, the inside of the tube is purged free of oxygen, allowing the entire area to be completely covered with argon gas. The weld cycle is preprogrammed and set in the machine, making the entire operation completely automatic. The electrode orbits around the weld seam on an internal gear while the head remains stationary and when the rotation is completed, the head can be opened and immediately removed from the welded section.

Hygienic Clamp Type Connection – This type of mechanical connection is the preferred alternative to the welded joint, and it is designed to be used in conjunction with clamp type tube ferrules and sanitary gaskets. These components (ferrules, gaskets, and clamps) are not designed or fabricated to any published national standard. Consequently, a large number of style variations are found throughout the industry. These differences may result in any number of technical deficiencies such as excessive ferrule flange bending stresses and/or lack of circumferential contact, leading to poor and irregular gasket compression. The ASME BPE is addressing the issues of standardization to establish dimensions and tolerances of the hygienic clamp type connection, including ferrules (external and internal, but not the sealing face), clamps (internal), and gaskets (as pertaining to the sealing surface and thickness). It is noted that ferrules, at the present time, may be fabricated in accordance to dimensional standards ISO 2852, BS 4825, or DIN 32676.

Stainless Steel Passivation

Passivation is a post-weld treatment and/or cleaning process used to restore (by introduction of oxygen) the thin chromium oxide (with some oxides of iron and nickel) film or passive layer that forms on stainless steel naturally when in contact with air. Methods and tests for cleaning and passivation of critical water, product, and process systems are described in ASTM A380 "*Standard Practice for Cleaning and Descaling Stainless Steel Parts, Equipment, and Systems*." Other ASTM Specifications address the passivation treatment for stainless steel parts (A967), and passivation of stainless steel using electropolishing (B912).

Passivation removes/dissolves free iron and other anodic contaminants from the surface of corrosion-resistant parts, leaving chromium and iron oxides as the primary metal components [5]. Because welding disturbs the passive layer by reducing the chromium and increasing the iron, thus altering the chrome/iron ratio (measure of corrosion resistance), upon completion and approval of the weld, the weld surface and adjacent boundary area must be brought back to a passive state. Also, certain normal operating conditions in typical WFI, RO, DI, clean/pure steam, some process systems, and in some rare cases, Clean-In-Place (CIP) systems often lead to formation of the most prevalent form of self-catalyzing corrosion called "rouge" [1] which is a colloidal form of iron oxide containing chromium and nickel in various forms. This problem may be accentuated by the use of high temperature, aggressive process chemicals, ultra pure water, and can be overcome only by restoring the surface to its passive state.

It must be noted that individual components in addition to whole systems that may include equipment, piping, and other components, can be passivated. Passivation of systems is required after system fabrication or erection, and at established intervals to ensure the passivity of the product/solution contact surfaces [See Electropolished (EP) Finishes].

Plastics

As the pharmaceutical and biotechnology industries confront challenges such as increased competition, consolidation, globalization, high R&D costs, and demanding manufacturing standards and guidelines, the need for the use of alternative materials of construction becomes a more significant issue. Despite the many advantages of stainless steel, the wide availability of plastics offering lower initial costs, less weight, complete resistance to corrosion, lower joining temperatures when welding, good thermal insulation, elimination of the passivation process, and extremely smooth internal, surfaces have increased their application, particularly in systems such as purified water distribution loops and other critical processes.

FDA requirements for pharmaceutical piping and equipment stipulate that materials must have low extractables, tolerance for sanitizing procedures and operating temperatures, and an interior surface smooth enough to resist microbial colonization. Design criteria for material selection include:

1. Wetted components that have smooth, non-porous surfaces

2. Joining methods for piping and lining that minimize crevices and discontinuities

3. Joining methods that minimize or eliminate the use of glues or solvents capable of migration into the water

4. Materials that are free of biological degradable substances that can be nutrient sources

5. Materials should not contain leachable additives, such as pigments

6. Surface smoothness measured in Ra and comparable to that of the stainless steels

Thermoplastic Polymers

Widely used in the biopharmaceutical industry, thermoplastic materials do not have cross-linked molecules, have a defined melting point; and can be melted, cooled, and remelted without destroying the physical or mechanical properties of the polymer. Thermoplastics are generally grouped into *amorphous* and *crystalline* materials. Crystalline polymers tend to be relatively strong and nonelastic, such as the polyvinyl chloride (PVC), polystyrene (PS), and polypropylene (PP). Amorphous thermoplastic materials show second-order transition temperature, at which the materials change from brittle to a more elastic form such as polyethylene (PE), polytetrafluoroethylene (PTFE), and polyvinylidene fluoride (PVDF).

Thermoset Polymers

Thermoset polymers have cross-linked molecules, no definite melting point, and can not be remelted. They are made from liquid monomers (or solutions containing monomers), formed into the desired shape, and polymerized by heat or chemical reaction. Thermosettings are ordinarily used in combination with higher strength inorganic reinforcements such as glass fiber. These composite materials are often called Fiberglass Reinforced Plastics (FRPs) or Reinforced Thermoset Resins (RTRs) such as epoxy, phenolic, polyurethane, silicone (hybrids of organic and inorganic materials), urea and melamine, polyester, vinyl ester, furan, and bisphenol A fumarate.

Polyolefin Polymers

Probably the most economical and widely used thermoplastics are the polyolefin polymers, which include such materials as polybutylene (PB), PP, and the various molecular weight PE.

Polypropylene (PP) [12] – Acrystalline polymer of special significance in both the food and the biopharmaceutical industries, offers as its key properties, a high heat resistance (for piping, an upper limit of 212°F), a specific gravity of 0.91 if unmodified (the lightest of the most common thermoplastics), stiffness, and chemical resistance to caustics, solvents, acids, and other organic chemicals. Its use is not recommended with strong oxidizing type acids, detergents, low boiling hydrocarbons, alcohols, and some chlorinated organic materials. Because PP is a relatively inert material and contributes little in the way of contamination to pharmaceutical water, it is highly suitable for piping systems. PP also has proved to be an excellent material for laboratory and industrial drainage where mixtures of acids, bases, and solvents are involved. PP is available in piping schedules 40 or 80 for pressure service and can be joined by socket solvent welding, thermo- seal fusion process, threading (Sch. 80 only), or flanging.

Fluoropolymers or Fluorinated Plastics

Fluorinated plastics are thermoplastic paraffinic polymers where the hydrogen has been replaced by fluorine and, in some cases, chlorine. Since their introduction more than 50 years ago, fluoropolymers have competed with metals, other polymers, glass, and elastomers to provide protection against corrosion in the chemical process industries (CPI).

Where fluoropolymer tubing is connected to other tubing materials, or other components such as a tee, elbow, reducer, or valve, various adaptors and procedures are available to create smooth, leak-proof connections. Fluoropolymer tubing can be connected to other tubing or fittings using welded sanitary clamp-type ferrules or flared fitting connectors, along with the specific sanitary gaskets and clamps.

Following are the most commonly used FDA-approved fluorinated plastics in high purity piping materials:

Polyvinylidene Fluoride (PVDF) [13] – PVDF is a strong, abrasion-resistant and wide temperature service range fluorocarbon material. Similar to PTFE, with the exception of not being fully fluorinated, it is a relatively inert material resistant to permeation of gases contributing little in the way of contamination to pharmaceutical water. It is chemically resistant to most acids, bases, and organic solvents and is ideally suited for handling wet or dry chlorine, bromine, and other halogens, but is unsuitable for handling strong alkalis, fuming acids, polar solvents, amines, ketones, and esters. It has a high tensile strength as well as a high heat deflection temperature. PVDF offers an extremely smooth surface finish (between 6 **R**a µin to 8 **R**a µin) and can be readily joined by the fusion process (free of internal beads or crevices), threading, or flanging.

Because of its high purity, low surface and joint extractables, and elevated temperature cleanability, natural unpigmented PVDF has become the most important alternative material for use in purified water distribution systems.

PVDF, however, has been used primarily in water systems that operate at ambient temperatures. There is some skepticism over the use of PVDF in hot WFI distribution loops; mainly because it has been observed that exposure to heat will discolor the material. The discoloration is the result of alterations to the chemical structure of PVDF on the atomic scale.

Polytetrafluoroethylene Resins (PTFE) [14] – Introduced in 1950, PTFE is a non-melt, fully fluorinated fluoropolymer resistant to practically every known chemical or solvent and possesses the highest useful temperature limit of commercially available plastics, and has an exceptionally low coefficient of friction, high impact strength, and low surface energy. Usual processing techniques like injection molding are not possible with PTFE; it must be compression-molded into block form and then machined into a finished product. PTFE resin is pressed into shapes under high pressure at room temperature and then heated to a range of 685°F to 720°F to complete the molding (sintering process) and adjust the crystalline content.

Because of its elastic recovery properties, PTFE, a self-lubricating compound, is used in sealing and flexing applications such as sanitary seals, valve diaphragms, hygienic gaskets, o-rings in mechanical seals, and seals and seats of stem and rotary valves such as ball valves. It is also commonly used as a liner or coating material for valves and pumps for the pharmaceutical industry.

Perfluoroalkoxy Resins (PFA) [14] – Of the melt-processible fluoropolymers, which are the most suitable for tubing, hoses, components of valves, etc., PFAprovides the extreme thermal and chemical resistance required in the biopharmaceutical processing. PFA, however, does not have the physical strength of PTFE at elevated temperatures and must be reinforced or designed with thickness to compensate for its softness. Tests have shown that among materials such as stainless steel, glass, silicon-coated glass, PP, and PVDF, even when proteins and microorganisms were added to more efficiently wet test surfaces, PFA was the least affected by contaminants and biofilm growth [8]. PFAhas been proven in CIP-SIP operations, purified water, WFI, and biopharmaceutical applications. Depending on the design, PTFE piping may use PFA fittings.

Elastomers

Elastomers are long chain copolymers (consisting of more than one monomer) or terpolymers (two or three different monomers in one chain) that contain adequate crosslinks among individual chains. These materials can be stretched or compressed repeatedly and, upon immediate release of stress, will return to their approximate original size. These materials are elastic.

Elastomer is another term that describes “rubber”. Rubber is any solid substance that, after being treated with a combination of sulphur, heat (vulcanization), and usually an organic accelerator (to shorten the time or lower the heat necessary for vulcanization), becomes elastic. The term “rubber” includes natural rubber and synthetic rubber, which is normally designated as elastomer. Some standards attempt to reserve the term elastomer for a crosslinked material but there is no general agreement on this issue. Consequentially, elastomer and rubber are used as synonyms.

Natural Rubber – Natural rubber is obtained from the milky secretion (latex) of various plants, but the only important source of natural rubber (sometimes called Pará rubber) is the tree *Hevea brasiliensis*. For most purposes the rubber is ground (to break the long polymer chains), dissolved in a suitable solvent, and compounded with other ingredients, e.g., fillers and pigments such as carbon black for strength and whiting for stiffening; antioxidants; plasticizers, usually in the form of oils, waxes, or tars; accelerators; and vulcanizing agents.

Synthetic Rubber – Synthetic rubbers, many of them copolymers, are made of raw material derived from petroleum, coal, oil, natural gas, and acetylene. The earliest synthetic rubbers were the styrene-butadiene copolymers, Buna Aand SBR, whose properties are closest to those of natural rubber.

Among the specialty elastomers are copolymers of acrylonitrile and butadiene that were originally called Buna-N and are now known as Nitrile elastomers or NBR rubbers. They have excellent resistance to petroleumbased oils and fuels, water, and alcohols. Butyl rubbers, copolymers of isobutylene and 1.3% isoprene; valuable because their good resistance to abrasion, low gas permeability, and high dielectric strength. Neoprene (polychloroprene), particularly useful at elevated temperatures and used for heavy-duty applications. Ethylene-propylene rubbers (RPDM) with their high resistance to weathering and sunlight. Urethane elastomers, called spandex and consisting of urethane blocks (for strength) and polyether or polyester blocks (for elasticity).

Sealing Materials

Seals are those elements that create or maintain process boundaries between system components and/or subassemblies in order to ensure system integrity in validated process and utility systems. Seals must be biocompatible (able to be in contact with bacteria or mammalian cells without interfering with their metabolism or ability to live and multiply), must be corrosion and permeation resistant, their surface finishes must be free of molding imperfections and foreign matter on surfaces within the sealing area, and shall not generate particulate that may entrain the product.

There are several parameters to be considered during the selection of appropriate seal materials:

1. Fluid Compatibility – Swell is the most common byproduct of chemical incompatibility in seals. Excessive swell can lead to extrusion of the seal through the opening in the mating surface.

2. Temperature Range – Although medical equipment and instrumentation are not often used in extreme temperature environments, some seals and gaskets may be exposed to significant temperature ranges. Elevated temperatures beyond the recommended limit of the seal material can result in extrusion of the component, compression set, or degradation.

3. Mechanical Requirements – Mechanical performance of seals involves a broad range of properties including service pressure, compression, abrasion resistance, and tear resistance.

The highest-priority parameters should drive the selection process. For example, if chemical resistance is the most critical parameter, this should be used to narrow the selection.

FDA-Compliant Elastomers

Listed below are the FDA-compliant elastomers utilized in accordance with CFR, Title 21, Chapter I, Part 177, Subpart B "*Substances for Use as Basic Components of Single and Repeated Use Food Contact Surfaces*." It must be noted that the term Food does not indicate exclusion of products and/or solutions used in the biopharmaceutical industry:

Ethylene-Propylene-Diene (EPDM) [15] – Anumber of different types of hydrocarbon rubber are available commercially. These products are based on ethylene, propylene, and ethylidene norbornene and are sold under two designations: IP (made in a solution base), and MG (made in a gas phase process). All are members of the broad family of EPDM polymers.

Many of the IP products are compliant with one or more of the following FDARegulations with use restrictions as defined in the Regulations: 21 CFR 177.2600, 21 CFR 177.1520, 21 CFR 175.105 "*Adhesives*", and 21 CFR 177.1210 "*Closures with sealing gaskets for food containers*."

EPDM is excellent for hot water and steam service up to 325°F. It is very abrasion resistant and has excellent resistance to ozone, sunlight or weather, and deionized water. EPDM also has good tensile strength and good resistance to mild acids, alkalis, and alcohols.

Buna-N or Nitrile Rubber (NBR) [15] – Buna-N is suitable for use with aromatic hydrocarbons, dilute acids and bases, mineral oils, and vegetable oils. Generally unsuitable for ozone, unsaturated halogen compounds, halogenated hydrocarbons, ketones, esters, aldehydes, chlorinated and nitro hydrocarbons or strong acids. Temperature limits -40°C to 105°C, and intermittently can withstand 120°C. Hydrogenated versions of these copolymers (HNBR) provide improved chemical and ozone-resistant elastomers.

Fluorine Rubber (FPM) (FKM) [15]– This fluorelastomeric rubber possesses good tensile strength, resilience, and low compression set; exhibits good mechanical, electrical, and weather-resistance properties, as well as ozone, oxygen, and flame resistance, and low gas permeability for use under extreme vacuum conditions. It does have excellent resistance to oils, fuels, lubricants, mineral acids, halogenated aromatic and aliphatic hydrocarbons such as carbon tetrachloride, toluene, benzene, and xylene, nonpolar compounds, oxidizing agents, and metalloid halides. It is not recommended for basic and oxygenated solvents such as ketones, ethers, esters, and ammonia or hot anhydrous, hydrofluoric, acetic, and chlorosulfuric acids. The product has poor serviceability in steam use and should not be used for this application.

Platinum-cured Silicon (pt-Si) [16] – A silicone group of elastomeric materials made from silicone, oxygen, hydrogen, and carbon. They have poor tensile strength, a high coefficient of friction, and possess excellent resistance to temperature extremes with 232°C being the maximum temperature recommended for continuous use with 316° C possible for short periods. Recommended for high aniline oils and chlorinated di-phenyls. Not recommended for most petroleum fluids, ketones, and steam.

Silicone elastomers are cured by either of two methods: peroxide curing or platinum curing. Peroxide-cured silicones hold their shape after repeated compression (good for tubing used in pumping operations); however, they require an additional postcure step to remove byproducts such as Polychlrorinated Biphenyls (PCBs) generated by the decomposition of the peroxide. In contrast, platinum curing provides very low levels of extractables without the postcure step. Platinum-catalyzed elastomers have higher tear strength but lack resilience and they lose their configuration after repeated compression (pump head applications).

In the medical device and pharmaceutical applications, two-part platinum- catalyzed (1:1 by weight) silicone elastomers are typically used in injection molding of precision and intricate parts of medical devices (Orings, gaskets, stoppers, and closures), mesh coating, fabrication of medical/ surgical/diagnostic devices and components, fabrication of extruded parts, and implantation applications.

Perfluorocarbon-cured elastomers KLR-6221, and KLR-6230 (FFKM) [17] – The referenced section of CFR, Title 21, describes identity, optional adjuvant substances, specifications, extractive limitations, and conditions of use for KLR-6221 and KLR-6230. KLR-6221 meets the test requirements of a USP Class VI polymer. USP testing was done to support use of KLR-6221 parts in pharmaceutical processing and food processing applications. While USP Class VI compliant materials are not required for pharmaceutical and food processing applications, many pharmaceutical and food processing customers have requested compliance.

KLR 6221 and 6230 offer excellent steam cycling resistance and reduce extractables from sealing materials to trace levels (not to exceed 0.2 mg/in^2), and provide superior chemical resistance. These compounds are especially suited for WFI systems, Steam-In-Place (SIP) cleaning, and other critical systems. Because the perfluorelastomer polymer in KLR- 6221 parts are fully saturated, it is also well suited for Ozonated Deionized Water service.

Unlike other elastomeric seals made with FDA-compliant elastomers, KLR-6221 perfluoroelastomers parts are thermally stable up to 260°C (500°F), permitting use in applications such as Stage II Sterilization processes, where other elastomers lose their sealing capabilities.

Perfluorocarbon Resins [14] – In general, because of their outstanding friction reduction, material release, chemical resistance, and thermal stability, fluoropolymers, specifically perfluoropolymers, have found increasing applications as materials of construction in the pharmaceutical and biotechnology industries. PTFE, PFA, and FEP fluoropolymer resins meet FDA regulations. Also, representative samples of these fluoropolymers have been tested in accordance with USP protocols and all meet the requirements of a USP Class VI plastic. While USP Class VI certification is not required for pharmaceutical processing, many pharmaceutical customers seeking ISO-9000 certification have requested it.

a) Polytetrafluoroethylene Resins (PTFE) – See Fluoropolymers or Fluorinated Plastics

b) Perfluoroalkoxy Resins (PFA) – See Fluoropolymers or Fluorinated Plastics

c) Fluorinated Ethylene Propylene Resins (FEP) – A melt-processible fluorinated ethylene propylene resin that meets the ASTM D2116- 95a "*Standard Specification for FEP – Fluorocarbon Molding and Extrusion Materials, 08.01*."

Regulatory Issues

United States Pharmacopeia (USP) Section <88>

In the United States Pharmacopeia, Biological Tests, Section <88> "*Biological Reactivity Tests, In Vivo*" the following three 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:

Systemic Injection Test – Test designed to evaluate systemic responses to the extracts of materials under test following injection into mice. Intracutaneous Test – Test designed to evaluate local responses to the extracts of materials under test following intracutaneous injection into rabbits.

Implantation Test – Test designed for the evaluation of plastic materials and other polymeric materials in direct contact with living tissue. 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. The *Implantation Test*, (Intramuscular implantation) 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.

Six Plastic Classes are defined, and the classification is based on responses to a series of in vivo tests for which extracts of samples, materials, and routes of administration are specified.

The choice of extractants (Sodium Chloride, 1 in 20 Solution of Alcohol in Sodium Chloride, Polyethylene Glycol 400, and Vegetable Oil) is representative of the vehicles of preparation with which the plastics are likely to be in contact.

With the exception of the *Implantation Test*, the procedures are based on the use of extracts that, depending on the heat resistance of the material, are prepared at one of three standard temperatures: 50°C (122°F), 70°C (158°F), and 121°C (249.8°F). Therefore, the class designation of a plastic must be accompanied by an indication of the temperature of extraction (e.g., IV-121°, which represents a class IV plastic extracted at 121°C, or I- 50°, which represents a class I plastic extracted at 50°C).

Conclusion

It is very clear to see that the biotechnology industry demands special care and attention in the selection of materials for the product contact surfaces as well as the solution contact surfaces. The emphasis has been placed principally in the cleanliness and corrosion resistance issues. To these purposes, a whole segment of the industry dedicates considerable time and effort in R&D for new materials and applications. Awareness and adherence to present codes and regulations, as well as knowledge of new and advanced technologies, are the keys to successful completion of design and engineering of systems utilizing these very valuable resources.

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11. ANSI/ASME B46.1 "Surface Texture - Surface Roughness, Waviness and Lay."

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13. CFR, Title 21, Chapter I, Part 177, Subpart B, Section 177.2510 "Polyvinylidene fluoride resins."

14. CFR, Title 21, Chapter I, Part 177, Subpart B, Section 177.1550 "Perfluorocarbon resins."

15. CFR, Title 21, Chapter I, Part 177, Subpart B, Section 177.2600 "Rubber articles intended for repeated use."

16. CFR, Title 21, Chapter I, Part 177, Subpart B, Section 177.2600, Subsection (c) (i) "Elastomers."

17. CFR, Title 21, Chapter I, Part 177, Subpart B, Section 177.2400 "Perfluorocarbon cured elastomers."

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