Designation: F3384 – 21

Standard Specification for Polydioxanone Polymer Resins for Surgical Implants[1]

This standard is issued under the fixed designation F3384; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 This specification covers virgin polydioxanone homopolymer resins intended for use in surgical implants.

1.2 Polydioxanone is commonly abbreviated as PDO, and is alternatively referred to as poly(para dioxanone) or poly(ρ-dioxanone) with the acronym PPD. Additionally, it may be referred to as PDS as it is the polymer of composition of PDS suture (Ethicon, Inc.), representing an early and widely used application of polydioxanone polymer.

1.3 This specification covers virgin polydioxanone resins able to be fully solvated at 30 °C by fluorinated solvents such as hexafluoroisopropanol (HFIP) or hexafluoroacetone (HFA).

1.4 Homopolymers of this composition are known to be semi-crystalline. Within this specification, semi-crystallinity within the resin is defined by the presence of a DSC (differential scanning calorimetry) crystalline endotherm peak upon annealing between 105 and 115 °C. While the presence of a crystalline endotherm indicates semi-crystallinity, the percentage and morphology of the crystalline phase are highly dependent on processing, and in particular on the thermal history of the material. Therefore, the thermal properties and percent crystallinity of the virgin polymer resin (with exception of melting temperature) are not necessarily indicative of final product quality.

1.5 This specification addresses material characteristics of the virgin polydioxanone-based resins intended for use in surgical implants and does not apply to packaged and sterilized finished implants fabricated from these materials, nor does it address the characteristics of polydioxanone resins with compounded materials such as dyes, polymeric or ceramic compounds, or any other additives.

1.6 As with any material, some characteristics may be altered by processing techniques (such as molding, extrusion, machining, assembly, sterilization, and so forth) required for the production of a specific part or device. Therefore, properties of fabricated forms of this resin should be evaluated independently using appropriate test methods to ensure safety and efficacy.

1.7 Biocompatibility testing is not a requirement since this specification is not intended to cover fabricated devices. While biocompatibility testing of resin may provide an early indication of potential safety, biocompatibility analysis of the final finished device is required to determine safety and suitability for any implant device. Refer to Supplementary Requirement S1 of this standard and Guide F2902 for relevant biocompatibility information.

1.8 The values stated in SI units are to be regarded as standard. No other units of measurement are included in this standard.

1.9 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety, health, and environmental practices and determine the applicability of regulatory limitations prior to use.*

1.10 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

D1505 Test Method for Density of Plastics by the Density-Gradient Technique

D2857 Practice for Dilute Solution Viscosity of Polymers

D3418 Test Method for Transition Temperatures and Enthalpies of Fusion and Crystallization of Polymers by Differential Scanning Calorimetry

D4603 Test Method for Determining Inherent Viscosity of Poly(Ethylene Terephthalate) (PET) by Glass Capillary Viscometer

D5296 Test Method for Molecular Weight Averages and

[1] This specification is under the jurisdiction of ASTM Committee F04 on Medical and Surgical Materials and Devices and is the direct responsibility of Subcommittee F04.11 on Polymeric Materials.

Current edition approved Dec. 1, 2021. Published December 2021. DOI: 10.1520/F3384-21.

[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

Molecular Weight Distribution of Polystyrene by High Performance Size-Exclusion Chromatography
E473 Terminology Relating to Thermal Analysis and Rheology
E793 Test Method for Enthalpies of Fusion and Crystallization by Differential Scanning Calorimetry
E794 Test Method for Melting And Crystallization Temperatures By Thermal Analysis
E967 Test Method for Temperature Calibration of Differential Scanning Calorimeters and Differential Thermal Analyzers
E968 Practice for Heat Flow Calibration of Differential Scanning Calorimeters
E1142 Terminology Relating to Thermophysical Properties
E1252 Practice for General Techniques for Obtaining Infrared Spectra for Qualitative Analysis
E1356 Test Method for Assignment of the Glass Transition Temperatures by Differential Scanning Calorimetry
E1994 Practice for Use of Process Oriented AOQL and LTPD Sampling Plans
E2977 Practice for Measuring and Reporting Performance of Fourier-Transform Nuclear Magnetic Resonance (FT-NMR) Spectrometers for Liquid Samples
F748 Practice for Selecting Generic Biological Test Methods for Materials and Devices
F1925 Specification for Semi-Crystalline Poly(lactide) Polymer and Copolymer Resins for Surgical Implants
F2902 Guide for Assessment of Absorbable Polymeric Implants

2.2 *ANSI Standards:*[3]
ANSI/ISO/ASQ 9000:2015 Quality Management Systems—Fundamentals and Vocabulary
ANSI/ISO/ASQ 9001:2015 Quality Management Systems—Requirements
ANSI/ISO/ASQ 13485:2016 Medical Devices—Quality Management Systems—Requirements for Regulatory Purposes

2.3 *Other Documents:*
ICH Q3C International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Quality Guideline: Impurities: Guideline for Residual Solvents[4]
ICH Q3D International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Quality Guideline: Guideline for Elemental Impurities[4]
ISO 10993-1 Biological Evaluation of Medical Devices[3]
ISO 11357 Plastics—Differential Scanning Calorimetry (DSC)[3]
ISO 80000-9 Quantities and Units—Part 9: Physical Chemistry and Molecular Physics[3]
21 CFR 820 United States Code of Federal Regulations, Title 21—Food and Drugs Services, Part 820—Quality System Regulation[5]
21 CFR 878.4840 Absorbable Polydioxanone Surgical (PDS) Suture[5]
21 CFR 74.3602 D&C Violet No. 2[5]
FDA Guidance Document Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process' – Guidance for Industry and Food and Drug Administration Staff[6]
USP United States Pharmacopeia, Edition 40[7]
USP <232> Elemental Impurities—Limits[7]
USP <233> Elemental Impurities—Procedures[7]
USP <788> Particulate Contamination[7]
NIST Special Publication SP811 Guide for the Use of the International System of Units (SI)[8]

3. Terminology

3.1 *Definitions:*

3.1.1 *virgin polymer, n*—the initially delivered form of a polymer as synthesized from its monomers and prior to any processing or fabrication into a medical device.

4. Materials and Manufacture

4.1 All raw monomer components and other materials contacting either the raw monomer(s) or resin product shall be of a quality suitable to allow use of such resin in the manufacture of an implantable medical product. Such quality includes adequate control of particles and other potential contaminants that may affect either the toxicity of or the cell response to the as-implanted or degrading final product.

4.2 All polymer manufacturing (including monomer handling, synthesis, pelletization/grinding, and all subsequent handling) shall be undertaken under conditions suitable to allow use of such resin in the manufacture of an implantable medical product.

4.3 Any additional additives, as agreed upon by the manufacturer and customer, shall be of a quality suitable to allow use in the manufacture of an implantable medical product. The presence, analysis, and reporting related to any additives is outside the scope of this standard specification.

4.4 Guidance related to the use of colorants (color additives) may be found through the US-FDA website: https://www.fda.gov/ForIndustry/ColorAdditives.

5. Chemical Composition

5.1 To ensure the attainment of the desired properties, the following tests shall be conducted with the requirements identified in Table 1.

[3] Available from American National Standards Institute (ANSI), 25 W. 43rd St., 4th Floor, New York, NY 10036, http://www.ansi.org.

[4] Available from ICH Seceretariat, c/o IFPMA, 30 rue de St-Jean, P.O. Box 758, 1211 Geneva 13, Switzerland. Available online at http://www.ich.org/LOB/media/MEDIA423.pdf.

[5] Available from U.S. Government Publishing Office (GPO), 732 N. Capitol St., NW, Washington, DC 20401, http://www.gpo.gov.

[6] Available from U.S. Food and Drug Administration (FDA), 10903 New Hampshire Ave., Silver Spring, MD 20993, http://www.fda.gov.

[7] Available from U.S. Pharmacopeial Convention (USP), 12601 Twinbrook Pkwy., Rockville, MD 20852-1790, http://www.usp.org.

[8] Available from National Institute of Standards and Technology (NIST), 100 Bureau Dr., Stop 1070, Gaithersburg, MD 20899-1070, http://www.nist.gov.

TABLE 1 Physical/Chemical Property Requirements for Virgin Polydioxanone Homopolymers

Analyte	Total Residual Monomer, (%)	Total Solvent Combination Residual(s)	Individual Solvent Residual(s) and Applicable ICH Limit(s) (in ppm)	(Optional) Residual Water (%)	Elemental Impurities, Limits (except catalyst)	Residual Catalyst (ppm)	Melting Temperature (°C)
Requirement	<2.0 % (by mass)	<0.5 % loss on drying	Report both for all solvent(s) utilized	≤0.5 % (by mass)[A]	Report conformance status per USP <232>[B]	Report per USP <233>[C]	105–115

[A] Utilizing a moisture determination method agreed upon by the supplier and purchaser.
[B] See 5.6.3.
[C] See 5.6.4 and X2.6.

5.2 *Chemical Identification:*

5.2.1 The identity of the virgin polymer shall be confirmed either by infrared, ^{1}H-NMR, or ^{13}C-NMR spectroscopy.

5.2.2 *Infrared Identification:*

5.2.2.1 Identity of polydioxanone homopolymer may be confirmed through an infrared spectrum exhibiting major absorption bands only at the wavelengths that appear in a suitable reference spectrum. Analysis shall be conducted using infrared spectroscopy practices similar to those described in Practice E1252. A typical infrared transmission reference spectrum for a polydioxanone homopolymer is shown in Fig. 1.

5.2.2.2 Additional or variable spectral bands may be indicative of sample crystallinity or either known or unknown impurities, including residual monomer, solvents, and catalysts (refer to the limits specified in Table 1).

5.2.3 *^{1}H-Nuclear Magnetic Resonance (^{1}H-NMR):*

5.2.3.1 Identity of PDO may be confirmed through sample dissolution, ^{1}H-NMR spectroscopy, and the use of a suitable reference spectrum. Sample dissolution is in deuterated hexafluoroisopropanol (d-HFIP) or other substantially proton-free solvent able to fully solvate the specimen without inducing competing spectral bands. Analysis shall be conducted using methods similar to those described in Practice E2977. A typical ^{1}H-NMR spectrum for PDO polymer is shown in Fig. 2.

5.2.3.2 Additional spectral bands may be indicative of known or unknown impurities, including residual monomer, solvents, and catalysts (refer to the limits specified in Table 1). A typical ^{1}H-NMR spectrum for PDO polymer containing residual monomer is shown in Fig. 3.

5.3 *Molar Mass:*

NOTE 1—The term molecular weight (abbreviated MW) is obsolete and

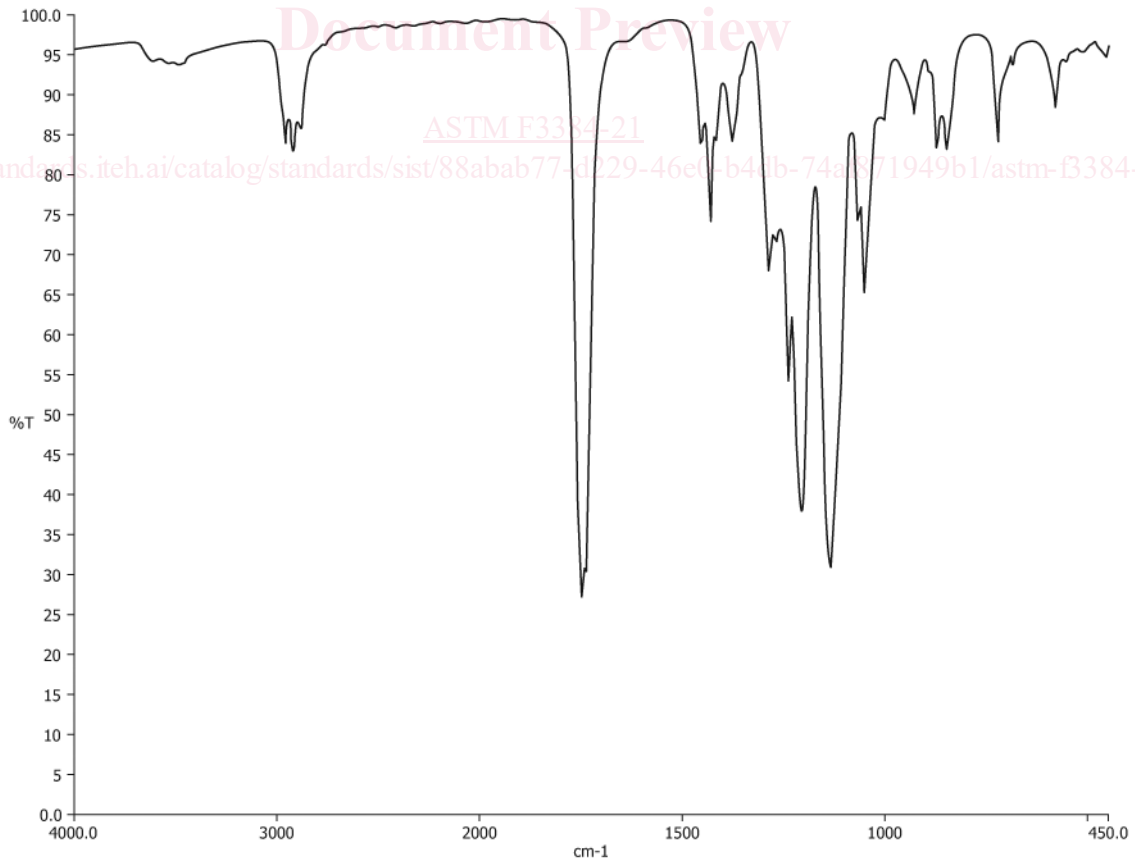

FIG. 1 Example Polydioxanone Resin Infrared Spectrum

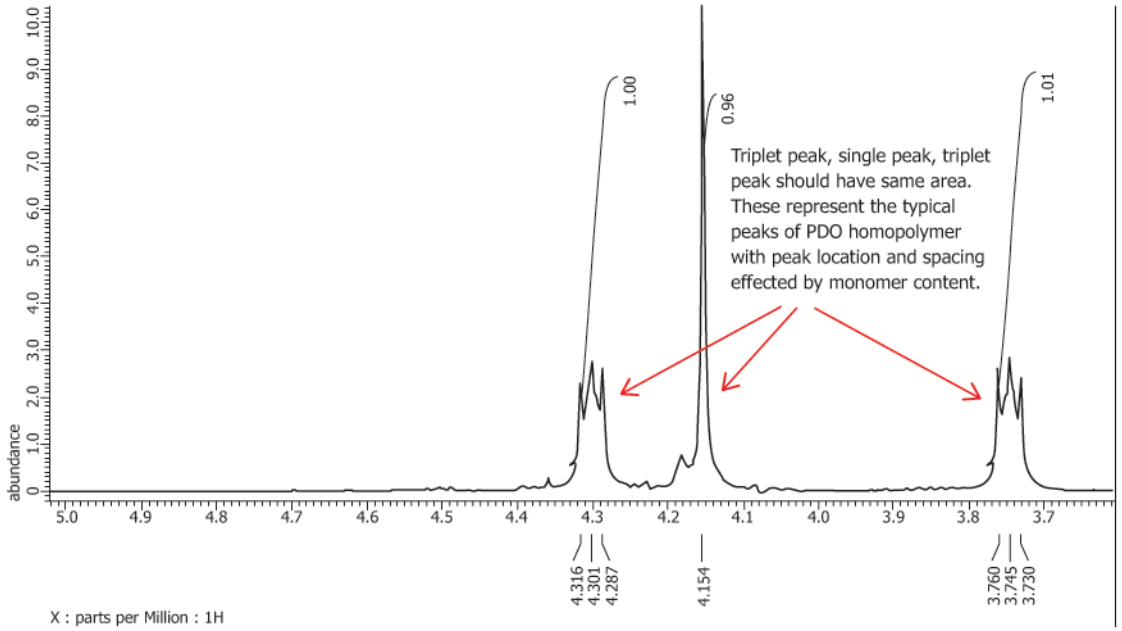

FIG. 2 Example Polydioxanone Resin ^{1}H-NMR Spectra

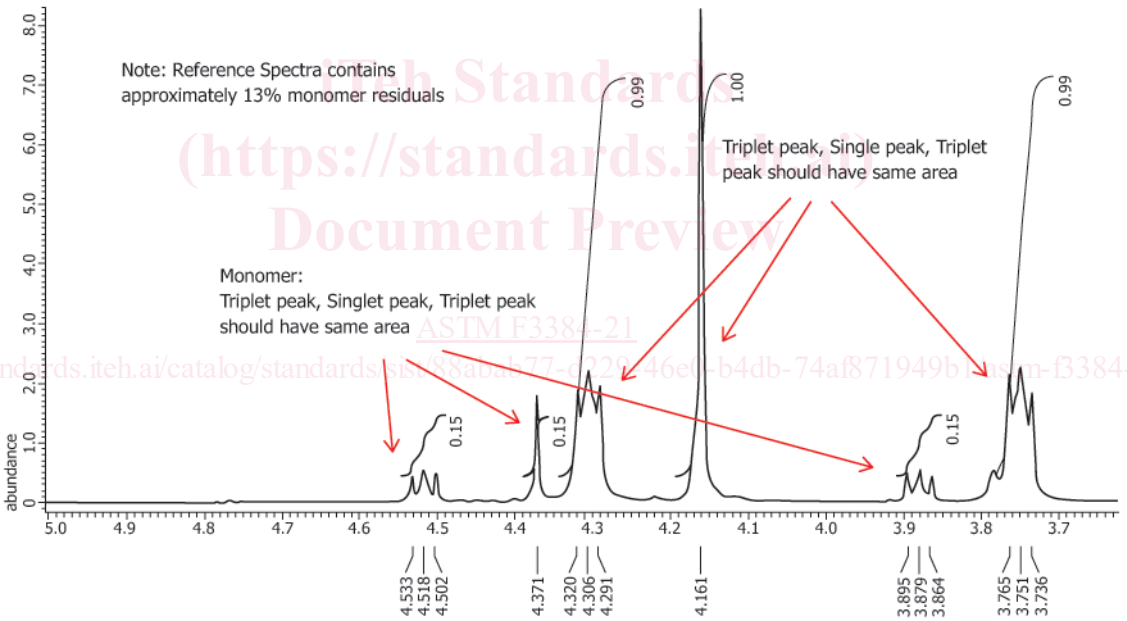

FIG. 3 Example ^{1}H-NMR Spectra of Polydioxanone Resin with Residual PDO Monomomer

should be replaced by the SI (Système Internationale) equivalent of either relative molecular mass (M_r), which reflects the dimensionless ratio of the mass of a single molecule to an atomic mass unit (see ISO 31-8), or molar mass (M), which refers to the mass of a mole of a substance and is typically expressed as grams/mole. For polymers and other macromolecules, use of the symbols M_w, M_n, and M_z continue, referring to mass-average molar mass, number-average molar mass, and z-average molar mass, respectively. For more information regarding proper utilization of SI units, see NIST Special Publication SP811.

5.3.1 The molar mass of the virgin polymer shall be indicated by inherent viscosity in dilute solution (IV). In addition to inherent viscosity (but not in place of), mass average molar mass and molar mass distributions may be determined by gel permeation chromatography (GPC) according to Test Method D5296, but using hexafluoroisopropanol (HFIP) or hexafluoroacetone (HFA) and appropriate calibration standards.

NOTE 2—Molar mass calibration standards (for example, polystyrene or polymethylmethacrylate) provide relative values only, and are not to be confused with an absolute determination of a dioxanone-based polymer's molar mass.

5.3.2 Determine the inherent viscosity of the polymer, preferentially in HFIP, at 30 °C using procedures similar to those described in Practice D2857 and Test Method D4603. Determination at a lower temperature of 25 °C is allowable, provided the utilized equipment delivers the required thermal

control and, if requested by the purchaser, an experimentally supported 30 °C equivalent concentration-appropriate extrapolated result is also reported within the supplied certification. If the required sample of the subject polymer ratio does not fully dissolve in HFIP, utilize HFA as the dissolution solvent. Note that any incomplete sample dissolution, precipitation from solution, or the formation of gels will produce inconsistency and variation in observed drop times.

NOTE 3—The IV test duration for each sample should be minimized to reduce the risk of resin concentration changes due to evaporative loss of solvent.

5.3.3 Inherent viscosity is determined utilizing the following:

$$IV = \frac{\ln(t / t_0)v}{W} \quad (1)$$

or

$$IV = \frac{\ln(t / t_0)}{C} \quad (2)$$

where:

IV = inherent viscosity (at 30 °C in dL/g),
t = efflux time in seconds for diluted solution,
t_0 = efflux time in seconds for source solvent,
W = mass of polymer being diluted (in grams),
v = dilution volume in deciliters (1 dL = 100 mL), and
C = concentration of dilute solution (w/v).

5.3.4 Resin concentration shall be 0.5 % w⁄v or less. When reporting results identify the solvent utilized, analyte concentration, and analysis temperature.

5.4 *Residual Monomer:*

5.4.1 The virgin polymer shall have a combined total residual monomer content ≤2.0 % in mass fraction. Alternatively, a purchaser may require a monomer content significantly less than 2 % to address processing and/or intended end-use requirements (see Supplementary Requirement S1).

5.4.2 Determine the mass fraction of residual monomer by gas chromatography, HPLC, ^{1}H-NMR spectroscopy (using deuterated hexafluoroisopropanol or other substantially proton-free solvent able to fully solvate the specimen), or other suitably sensitive analytic method as agreed upon by the supplier and purchaser.

5.5 *Residual Solvents:*

5.5.1 If any solvent is utilized in any resin manufacturing or purification step, determine residual levels of any utilized solvent(s) by gas chromatography or other suitable method as agreed upon by the supplier and purchaser. Acceptable residual levels of a particular solvent shall be reflective of toxicity, with a maximum acceptable limit consistent with ICH Q3C(R5). The detection limit for the chosen analytic method must be adequate to ensure compliance with the applicable ICH guideline, and the determined residual(s) and applied concentration limit(s) shall be reported. If no ICH concentration guideline has been established for a utilized solvent, an entry of "no ICH guidance available" shall be reported in lieu of a limit.

5.5.2 To minimize the potential for toxic interaction of solvent combinations, cumulative total solvent combination residuals shall be limited to <0.5 % loss on drying (refer to the limit specified in Table 1). Individual limits for common process solvents shall also be included, and the presence of any one or more solvent may vary by manufacturer. This limit is based on the ICH Q3C quality guidelines for materials where Class 2 and Class 3 solvents may be present. Potential inclusion of alternative solvents should be noted and applicable limits specified.

5.6 *Elemental Impurities:*

5.6.1 The significance of elemental impurities within an absorbable polymer is ultimately dependent on the dimensional characteristics of the final product and the rate of release of those initially interstitial elements into the surrounding tissue and extracelluar fluid. Thus, any risk assessment of such impurities will be dependent on the final product design and intended application. Consequently, this raw material (not final device) standard provides for appropriate reporting of elemental impurities values, but does not mandate any specific performance requirements. More detailed and pharmaceutical-oriented guidance regarding the appropriate means for both monitoring and assessing relevant elemental impurities within a final product can be found in USP Chapters <232> and <233> and in ICH Q3D.

5.6.2 Determine the concentration of the respective elemental impurities within the absorbable polymer by utilizing inductively coupled plasma mass spectroscopy (ICP-MS) or inductively coupled plasma atomic or optical emission spectroscopy (ICP-AES or ICP-OES) or an equivalent alternative method as described in Chapter <233> of the U.S. Pharmacopeia. The specific 24 different elemental impurities of interest are outlined in both USP <232> and in Table A.2.2 of ICH Q3D. Both of these documents include risk-based approaches toward the assessment and control of elemental impurities.

5.6.3 Except for elements intentionally added as catalysts, assess the obtained results for compliance with the parenteral concentration limits described within the individual component option of USP <232>, Table 3 (derived from ICH Q3D Option 1, Table A.2.2). If all listed elements, except for those added as catalysts, can be ensured to be maintained within the parenteral concentration individual component option limits, the resin "conforms" to the USP <232> elemental impurities limits (except catalyst). If any listed element (other than added catalyst) cannot be controlled to be maintained within the described USP <232> limits, the resin does not conform with USP <232> (except catalyst) and the concentration (in ppm, per USP <233> or equivalent) of each uncontrolled element is to be both monitored and reported.

5.6.4 For each element intentionally added as catalyst, the concentration (in ppm, per USP <233> or equivalent) is to be both monitored and reported.

5.7 *Residual Catalyst:*

5.7.1 Determine the amount of residual tin (Sn) by atomic absorption/emission (AA) spectroscopy or inductively coupled plasma (ICP) spectroscopy. If a catalyst other than tin is utilized, suitable methods to both determine and report residue shall be utilized.