



Designation: F1925 – 22

# Standard Specification for Semi-Crystalline Poly(lactide) Polymer and Copolymer Resins for Surgical Implants<sup>1</sup>

This standard is issued under the fixed designation F1925; 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 ( $\epsilon$ ) indicates an editorial change since the last revision or reapproval.

## 1. Scope

1.1 This specification covers virgin semi-crystalline poly(L-lactide) or poly(D-lactide) homopolymer resins intended for use in surgical implants. This specification also covers semi-crystalline resins of L-lactide copolymerized with other bioabsorbable monomers including, but not limited to, glycolide, D-lactide, and DL-lactide. The poly(L-lactide) or poly(D-lactide) based homopolymers and copolymers covered by this specification possess lactide segments of sufficient length to allow potential for their crystallization upon annealing.

1.2 Since poly(glycolide) is commonly abbreviated as PGA for poly(glycolic acid) and poly(lactide) is commonly abbreviated as PLA for poly(lactic acid), these polymers are commonly referred to as PGA, PLA, and PLA:PGA resins for the hydrolytic byproducts to which they respectively degrade. PLA is a term that carries no stereoisomeric specificity and therefore encompasses both the amorphous atactic/syndiotactic DL-lactide based polymers and copolymers as well as the isotactic D-PLA and L-PLA moieties, each of which carries potential for crystallization. Inclusion of stereoisomeric specificity within the lactic acid based acronyms results in the following: poly(L-lactide) as PLLA for poly(L-lactic acid), poly(D-lactide) as PDLA for poly(D-lactic acid), and poly(DL-lactide) as PDLA for poly(DL-lactic acid).

1.3 This specification is applicable to lactide-based polymers or copolymers that possess isotactic polymeric segments sufficient in size to carry potential for lactide-based crystallization. Such polymers typically possess nominal mole fractions that equal or exceed 50 % L-lactide. This specification is particularly applicable to isotactic-lactide based block copolymers or to polymers or copolymers synthesized from combinations of D-lactide and L-lactide that differ by more than 1.5 total mole percent (1.5 % of total moles). This specification is not applicable to lactide-co-glycolide copolymers with glycolide mole fractions greater than or equal to 70 % (65.3 % in

mass fraction), which are covered by Specification F2313. This specification is not applicable to amorphous polymers or copolymers synthesized from combinations of D-lactide and L-lactide that differ by less than 1.5 total mole percent (1.5 % of total moles) as covered by Specification F2579.

1.4 This specification covers virgin semi-crystalline poly(lactide)-based resins able to be fully solvated at 30 °C by either methylene chloride (dichloromethane) or chloroform (trichloromethane). This specification is not applicable to lactide:glycolide copolymers that possess glycolide segments sufficient in size to deliver potential for glycolide-based crystallization, thereby requiring fluorinated solvents for complete dissolution under room temperature conditions (see Specification F2313).

1.5 Within this specification, semi-crystallinity within the resin is defined by the presence of a DSC (differential scanning calorimetry) crystalline endotherm after annealing above the glass transition temperature. While other copolymeric segments may also crystallize upon annealing (for example, glycolide), specific characterization of crystalline structures other than those formed by lactide are outside the scope of this specification.

1.6 This specification addresses material characteristics of the virgin semi-crystalline poly(lactide)-based resins intended for use in surgical implants and does not apply to packaged and sterilized finished implants fabricated from these materials.

1.7 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.

1.8 Biocompatibility testing is not a requirement since this specification is not intended to cover fabricated devices.

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

1.10 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the*

<sup>1</sup> 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.

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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.

1.11 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:<sup>2</sup>

- D1505 Test Method for Density of Plastics by the Density-Gradient Technique
- D2857 Practice for Dilute Solution Viscosity of Polymers
- D3417 Test Method for Enthalpies of Fusion and Crystallization of Polymers by Differential Scanning Calorimetry (DSC) (Withdrawn 2004)<sup>3</sup>
- 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 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
- F2313 Specification for Poly(glycolide) and Poly(glycolide-co-lactide) Resins for Surgical Implants with Mole Fractions Greater Than or Equal to 70 % Glycolide

- F2579 Specification for Amorphous Poly(lactide) and Poly(lactide-co-glycolide) Resins for Surgical Implants
- F2902 Guide for Assessment of Absorbable Polymeric Implants

### 2.2 ANSI Standards:<sup>4</sup>

- ANSI/ISO/ASQ Q9000-2000 Quality Management Systems—Fundamentals and Vocabulary
- ANSI/ISO/ASQ Q9001-2000 Quality Management Systems—Requirements
- ANSI/ISO/ASQ 13485 Medical Devices—Quality Management Systems—Requirements for Regulatory Purposes

### 2.3 ISO Standards:<sup>5</sup>

- ISO 80000-9 Quantities and Units—Part 9: Physical chemistry and molecular physics
- ISO 10993 Biological Evaluation of Medical Devices<sup>4</sup>
- ISO 11357 Plastics—Differential Scanning Calorimetry (DSC)<sup>4</sup>

### 2.4 Code of Federal Regulations:<sup>6</sup>

- 21 CFR 820 United States Code of Federal Regulations, Title 21—Food and Drugs Services, Part 820—Quality System Regulation

### 2.5 United States Pharmacopeia:<sup>7</sup>

- USP, 26th Edition United States Pharmacopeia
- USP <232> Elemental Impurities—Limits
- USP <233> Elemental Impurities—Procedure
- USP <781> Physical Tests—Optical Rotation
- USP <788> Particulate Matter in Injections

### 2.6 NIST Publication:<sup>8</sup>

- NIST Special Publication SP811 Guide for the Use of the International System of Units (SI)

### 2.7 Other Documents:<sup>9</sup>

- ICH Q3C(R5) International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Quality Guideline: Impurities: Residual Solvents
- ICH Q3D(R4) International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guideline for Elemental Impurities

## 3. Terminology

### 3.1 Definitions:

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

<sup>5</sup> Available from International Organization for Standardization (ISO), ISO Central Secretariat, BIBC II, Chemin de Blandonnet 8, CP 401, 1214 Vernier, Geneva, Switzerland, <http://www.iso.org>.

<sup>6</sup> Available from U.S. Government Printing Office Superintendent of Documents, 732 N. Capitol St., NW, Mail Stop: SDE, Washington, DC 20401, <http://www.access.gpo.gov>.

<sup>7</sup> Available from U.S. Pharmacopeia, 12601 Twinbrook Pkwy., Rockville, MD 20852 or through <http://www.usp.org/products/USPNF/>. The standards will be listed by appropriate USP citation number. Succeeding USP editions alternately may be referenced.

<sup>8</sup> Available from National Institute of Standards and Technology (NIST), 100 Bureau Dr., Stop 1070, Gaithersburg, MD 20899-1070, at <http://physics.nist.gov/cuu/Units/bibliography.html>.

<sup>9</sup> Available from ICH Secretariat, c/o IFFMA, 30 rue de St-Jean, P.O. Box 758, 1211 Geneva 13, Switzerland. Available online at <http://www.ich.org/LOB/media/MEDIA423.pdf>.

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

<sup>3</sup> The last approved version of this historical standard is referenced on [www.astm.org](http://www.astm.org).

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 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 The semi-crystalline poly(lactide) polymers and copolymers covered by this specification shall be composed of either D-lactide or L-lactide in segments of sufficient length to allow crystallization. Copolymers covered by this specification can be of variable copolymer ratios and shall be composed of crystallizable lengths of D-lactide and/or L-lactide in combina-

tion with glycolide or other monomers where the glycolide mole fraction is less than 70 % (65.3 % in mass fraction). To ensure such composition and the attainment of the desired properties, the following tests shall be conducted.

##### 5.2 Chemical Identification:

5.2.1 The identity of the virgin polymer shall be confirmed either by infrared, <sup>1</sup>H-NMR, or <sup>13</sup>C-NMR spectroscopy.

##### 5.2.2 Infrared Identification:

5.2.2.1 Identity of semi-crystalline poly(lactide) homopolymer or poly(lactide)-based copolymer 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 methods similar to those described in Practice E1252. A typical infrared transmission reference spectrum for an L-PLA homopolymer is shown in Fig. 1. While poly(lactide)-based copolymers will each have their own respective spectrum that will vary in response to copolymer ratio, this analytic method typically lacks sensitivity sufficient for quantification of copolymer ratio as specified in 7.1.2.

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 limits specified in Table 1).

5.2.2.3 Since an infrared spectrum cannot distinguish between the different lactide stereoisomers (that is, poly(L-lactide) versus poly(D-lactide)), it is utilized here only as a

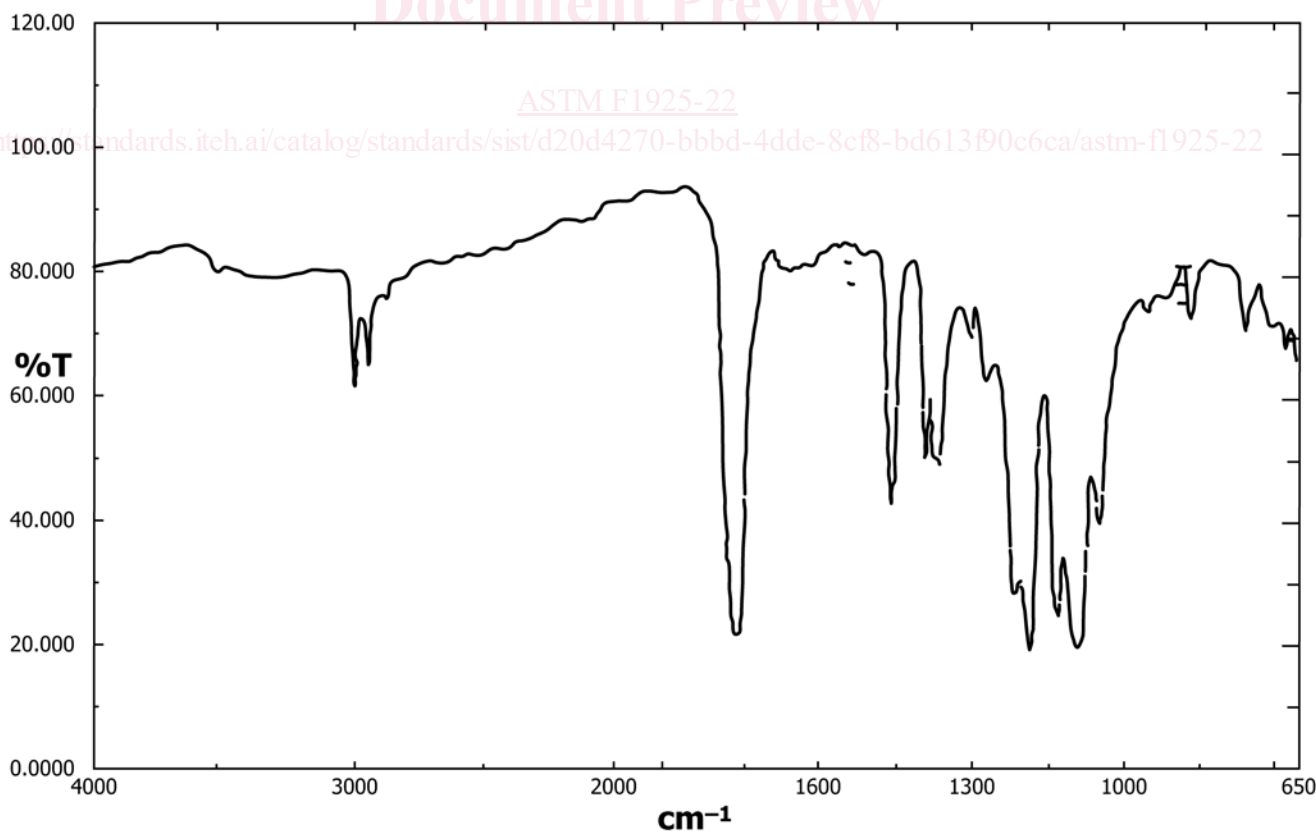


FIG. 1 Poly(L-lactide) Resin Infrared Spectrum

**TABLE 1 Physical/Chemical Property Requirements for Virgin Semi-Crystalline Poly(lactide) Homopolymers and Poly(lactide)-Based Copolymer Resins**

Analyte	Total Residual Monomer, (%)	Total Solvent Combination Residual(s) (in ppm)	Individual Solvent Residual(s) and Applicable ICH Limit(s) (in ppm)	(Optional) Residual Water (%)	Elemental Impurities (except catalyst)	Residual Catalyst (in ppm)	Copolymer Ratio	Specific Rotation
Requirement	<2.0 % <sup>A</sup> (by mass)	<1000 ppm	Report both for all solvent(s) utilized	≤0.5 % (by mass) <sup>B</sup>	Report conformance per USP <232> <sup>C</sup>	Report per USP <233> <sup>D</sup>	±3 % of target (by mole)	155° to 160°; (– for L-lactide; + for D-lactide; copolymers proportionate; see 5.3)

<sup>A</sup> Up to 3 % if deemed acceptable by the purchaser (see 5.5.1).

<sup>B</sup> Utilizing a moisture determination method agreed upon by the supplier and purchaser.

<sup>C</sup> See 5.7.3.

<sup>D</sup> See 5.7.4 and Note 4.

means of identifying the non-stereospecific poly(lactide) component of the semi-crystalline poly(lactide)-based polymer or copolymer.

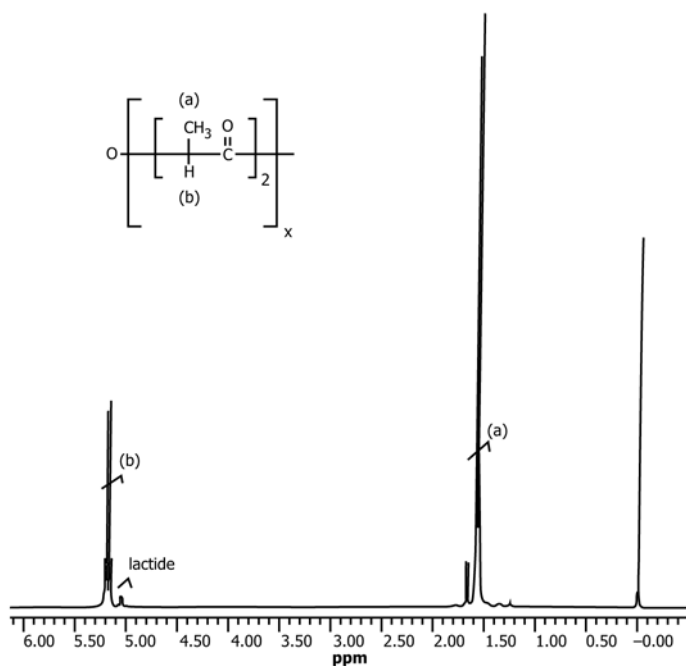
**5.2.3 Proton Nuclear Magnetic Resonance (<sup>1</sup>H-NMR) Identification:**

5.2.3.1 Identity of semi-crystalline poly(lactide) homopolymer or poly(lactide)-based copolymer may be confirmed through sample dissolution, <sup>1</sup>H-NMR spectroscopy, and the use of a suitable reference spectrum. Sample dissolution is in either deuterated chloroform, deuterated dichloromethane (methylene chloride), 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 proton NMR reference spectrum for an L-PLA homopolymer (with residual lactide monomer peak noted) 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).

**5.2.4 Carbon-13 Nuclear Magnetic Resonance (<sup>13</sup>C-NMR) Identification:**

ASTM F1925  
<https://standards.iteh.ai/catalog/standards/sist/d20d4270-bb6d-4613-90c6ca/astm-f1925-22>



**FIG. 2 Poly(L-lactide) Resin <sup>1</sup>H-NMR Spectrum**

5.2.4.1 Identity of semi-crystalline poly(lactide) homopolymer or poly(lactide)-based copolymer may be confirmed in a solid state through <sup>13</sup>C-NMR spectroscopy and the use of a suitable reference spectrum. Analysis shall be conducted using methods similar to those described in Practice E2977.

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

**5.3 Specific Rotation:**

5.3.1 Virgin poly(L-lactide) or poly(D-lactide) homopolymers shall have a specific rotation of –155° to –160° and +155° to +160°, respectively, when measured in either chloroform or methylene chloride at 20 °C using a polarimetry method equal to or equivalent to the Optical Rotation procedure described in USP <781>. Block copolymers of poly(L-lactide:D-lactide) may possess a reduced level of specific rotation proportioned to the copolymerization ratio. In no situation shall a resin covered by this specification possess a specific rotation value of less than 2.5 (that is, between –2.5 and +2.5), which is considered to be indicative of an amorphous polymer covered under Specification F2579.

**5.4 Molar Mass:**

NOTE 1—The term molecular weight (abbreviated MW) is obsolete and should be replaced by the SI (Système Internationale) equivalent of either relative molecular mass (*M<sub>r</sub>*), which reflects the dimensionless ratio of the mass of a single molecule to an atomic mass unit (see ISO 80000-9), 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<sub>w</sub>*, *M<sub>n</sub>*, and *M<sub>z</sub>* 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.

5.4.1 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 chloroform, dichloromethane, or hexafluoroisopropanol (HFIP) 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 lactide-based polymer's molar mass.

5.4.2 Determine the inherent viscosity of the polymer, preferentially in chloroform 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 copolymer ratio does not fully dissolve in chloroform, alternatively utilize either dichloromethane (methylene chloride) or HFIP 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 risk of resin concentration changes due to evaporative loss of solvent.

5.4.3 Inherent viscosity is determined utilizing the following:

$$IV = \frac{\ln(t/t_o)v}{w} \quad \text{or} \quad \frac{\ln(t/t_o)}{C} \quad (1)$$

where:

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

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

### 5.5 Residual Monomer:

5.5.1 The virgin polymer shall have a combined total residual monomer content less than or equal to 2.0 % in mass fraction. Residual monomer levels up to 3 % are acceptable if deemed by the purchaser to be suitable for the intended end-use application. Alternatively, a purchaser may require a monomer content significantly less than 2 % to address processing and/or intended end-use requirements (see Section S1—Biocompatibility).

5.5.2 Determine the mass fraction of residual monomer by gas chromatography, HPLC, <sup>1</sup>H-NMR spectroscopy (using deuterated chloroform, deuterated dichloromethane, 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.

### 5.6 Residual Solvents:

5.6.1 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.

5.6.2 To minimize the potential for toxic interaction of solvent combinations, cumulative Total Solvent Combination Residuals shall be limited to 1000 ppm (refer to the limit specified in **Table 1**). This limit carries the effect of allowing ICH Q3C quality guidelines when a single solvent system is utilized and less than 1000 ppm when combinations of more than one solvent are utilized (regardless of individual solvent toxicity).

### 5.7 Elemental Impurities:

5.7.1 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 extracellular 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 impurity 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 <232> and <233> and in the ICH Harmonised Guideline for Elemental Impurities, Q3D.

5.7.2 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 USP <233>. The specific 24 different elemental impurities of interest are outlined in both USP <232> and in Table A.2.2 of the ICH Harmonised Guideline for Elemental Impurities, Q3D (Dec 2014). Both of these documents include risk-based approaches toward the assessment and control of elemental impurities.

5.7.3 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 USP <232> (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.

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

### 5.8 Residual Catalyst (Optional):

5.8.1 Determine the amount of residual tin (Sn) by a method described in USP <233>. If a catalyst other than tin is utilized, suitable methods to both determine and report residue shall be utilized.