Designation: F2579 – 18

Standard Specification for Amorphous Poly(lactide) and Poly(lactide-co-glycolide) Resins for Surgical Implants[1]

This standard is issued under the fixed designation F2579; 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 amorphous poly(lactide) homopolymer and poly(lactide-co-glycolide) copolymer resins intended for use in surgical implants. The poly(DL-lactide) homopolymers covered by this specification are considered to be amorphous (that is, void of crystallinity) and are polymerized either from *meso*-lactide or from equimolar (racemic) combinations of D-lactide and L-lactide. The poly(DL-lactide-co-glycolide) copolymers covered by this specification are also considered to be amorphous and are co-polymerized from a combination of glycolide and either meso-lactide or racemic quantities of D-lactide and L-lactide, and typically possess nominal mole fractions that equal or exceed 50 % lactide.

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. Therefore, specific reference to DL-PLA is essential to appropriately differentiate the amorphous atactic/syndiotactic DL-lactide-based polymers and copolymers covered by this specification. Thus, 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 PDLLA for poly(DL-lactic acid).

1.3 This specification covers virgin amorphous 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-based polymers or copolymers that possess isotactic polymeric segments sufficient in size to carry potential for lactide-based crystallization, which are covered by Specification F1925 and typically possess nominal mole fractions that equal or exceed 50 % L-lactide. This specification is not applicable to lactide-co-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. This specification is specifically 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 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).

1.4 This specification addresses material characteristics of both poly(DL-lactide) and poly(DL-lactide-co-glycolide) resins intended for use in surgical implants and does not apply to packaged and sterilized finished implants fabricated from these materials.

1.5 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 assure safety and efficacy.

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

1.7 *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.*

1.8 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the*

[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.

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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

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

E1252 Practice for General Techniques for Obtaining Infrared Spectra for Qualitative Analysis

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

F2313 Specification for Poly(glycolide) and Poly(glycolide-co-lactide) Resins for Surgical Implants with Mole Fractions Greater Than or Equal to 70 % Glycolide

F2902 Guide for Assessment of Absorbable Polymeric Implants

2.2 *ANSI Standards:*[3]

ANSI/ISO/ASQ 13485 Medical devices -- Quality management systems -- Requirements for regulatory purposes

ANSI/ISO/ASQ Q9000 Quality Management Systems, Fundamentals and Vocabulary

ANSI/ISO/ASQ Q9001 Quality Management Systems, Requirements

2.3 *ISO Standards:*[3]

ISO 10993 Biological Evaluation of Medical Devices

ISO 80000-9 Quantities and units -- Part 9: Physical chemistry and molecular physics

2.4 *U. S. Pharmacopeia (USP) Standards:*[4]

USP 231 United States Pharmacopeia: Chemical Analysis – Heavy Metals

USP 232 United States Pharmacopeia: Elemental Impurities – Limits

USP 233 United States Pharmacopeia: Elemental Impurities – Procedures

USP 781 United States Pharmacopeia: Physical Tests – Optical Rotation

USP 788 United States Pharmacopeia: Particulate Matter in Injections

2.5 *Other Documents/Websites:*

ICH Q3C International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Quality Guideline: Impurities: Residual Solvents[5]

ICH Q3D International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guideline for Elemental Impurities[5]

21 CFR 820 Code of Federal Regulations, Title 21, Part 820, Quality System Regulation[6]

NIST Special Publication SP811 Guide for the Use of the International System of Units (SI)[7]

FDA Guidance "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.

3. Terminology

3.1 *Definitions:*

3.1.1 *virgin polymer*—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 for 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 steps) shall be undertaken under conditions suitable to allow for use of such resin in the manufacture of an implantable medical product.

5. Chemical Composition

5.1 The amorphous poly(DL-lactide) polymers covered by this specification shall be composed either of *meso* -lactide or a racemic combination of D-lactide and L-lactide. The amorphous poly(DL-lactide-co-glycolide) copolymers covered by this specification can be of variable copolymer ratios and shall

[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.

[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 U.S. Pharmacopeia (USP), 12601 Twinbrook Pkwy., Rockville, MD 20852-1790, http://www.usp.org.

[5] Available from ICH Secretariat, c/o IFPMA, 30 rue de St-Jean, P.O. Box 758, 1211 Geneva 13, Switzerland. Available online at http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html.

[6] 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.

[7] 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.

be composed of a combination of glycolide and either *meso*-lactide or a racemic combination of D-lactide and L-lactide where the glycolide mole fraction is less than 70 % (65.3 % in mass fraction). To assure such composition and the attainment of the desired properties, the following tests are to be conducted.

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 either poly(lactide) homopolymer or poly(lactide-co-glycolide) 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 and a typical infrared absorption reference spectrum for DL-PLA homopolymer are shown in Fig. 1, with example spectra for copolymers presented in Fig. 2. While poly(lactide-co-glycolide) 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, it is utilized here only as a means of identifying the non-stereospecific poly(lactide) component of a poly(lactide)-based polymer or copolymer.

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

5.2.3.1 Identity of either poly(lactide) homopolymer or poly(lactide-co-glycolide) copolymer may be confirmed through sample dissolution, ^{1}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. Typical proton NMR reference spectra for 100 % DL-PLA homopolymer and 85 % DL -PLA:15 % PGA copolymer are shown in Fig. 3 and Fig. 4, respectively.

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

5.2.4 *Carbon-13 Nuclear Magnetic Resonance (^{13}C-NMR) Identification:*

5.2.4.1 Identity of either poly(lactide) homopolymer or poly(lactide-co-glycolide) copolymer may be confirmed in a solid state through ^{13}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 The virgin homopolymer or copolymer shall have a specific rotation of –2.5 to +2.5 degrees when measured in either chloroform, methylene chloride, or tetrahydrofuran at 20°C using a polarimetry method equal to or equivalent to the Optical Rotation procedure described in USP <781>.

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_r), 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_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.

5.4.1 The molar mass of the virgin polymer shall be indicated by inherent viscosity (IV) in dilute solution. In addition to inherent viscosity (but not in place of), mass average molar mass and molar mass distributions maybe determined by gel permeation chromatography (GPC) according to the general procedure described in Test Method D5296, but using either chloroform or dichloromethane 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 dichloromethane (methylene chloride) 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.

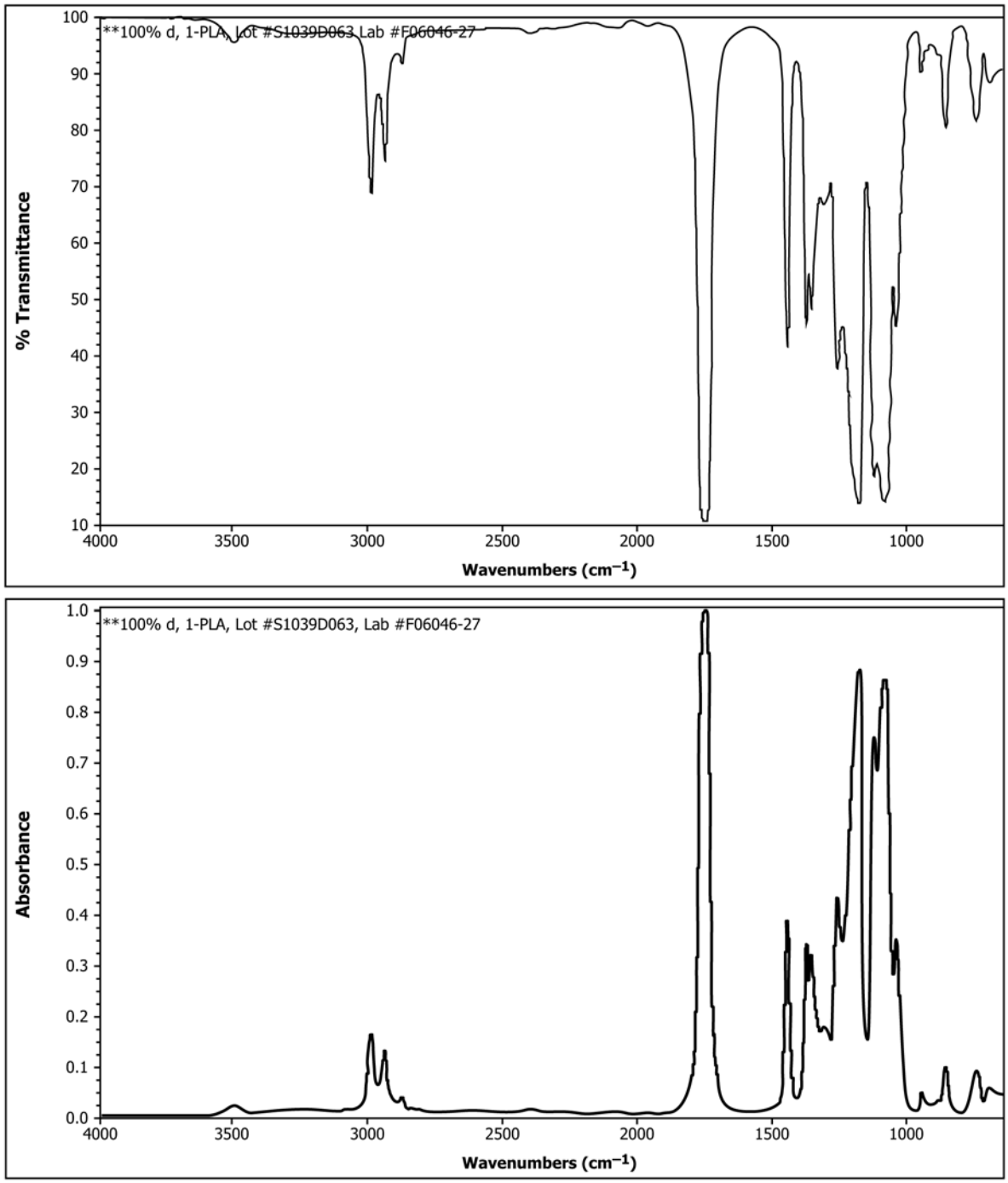
NOTE 3—The IV test duration for each sample should be minimized to reduce risk of resin concentration changes due to evaporative loss of solvent.

5.4.3 Inherent viscosity is determined utilizing the following:

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

or

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



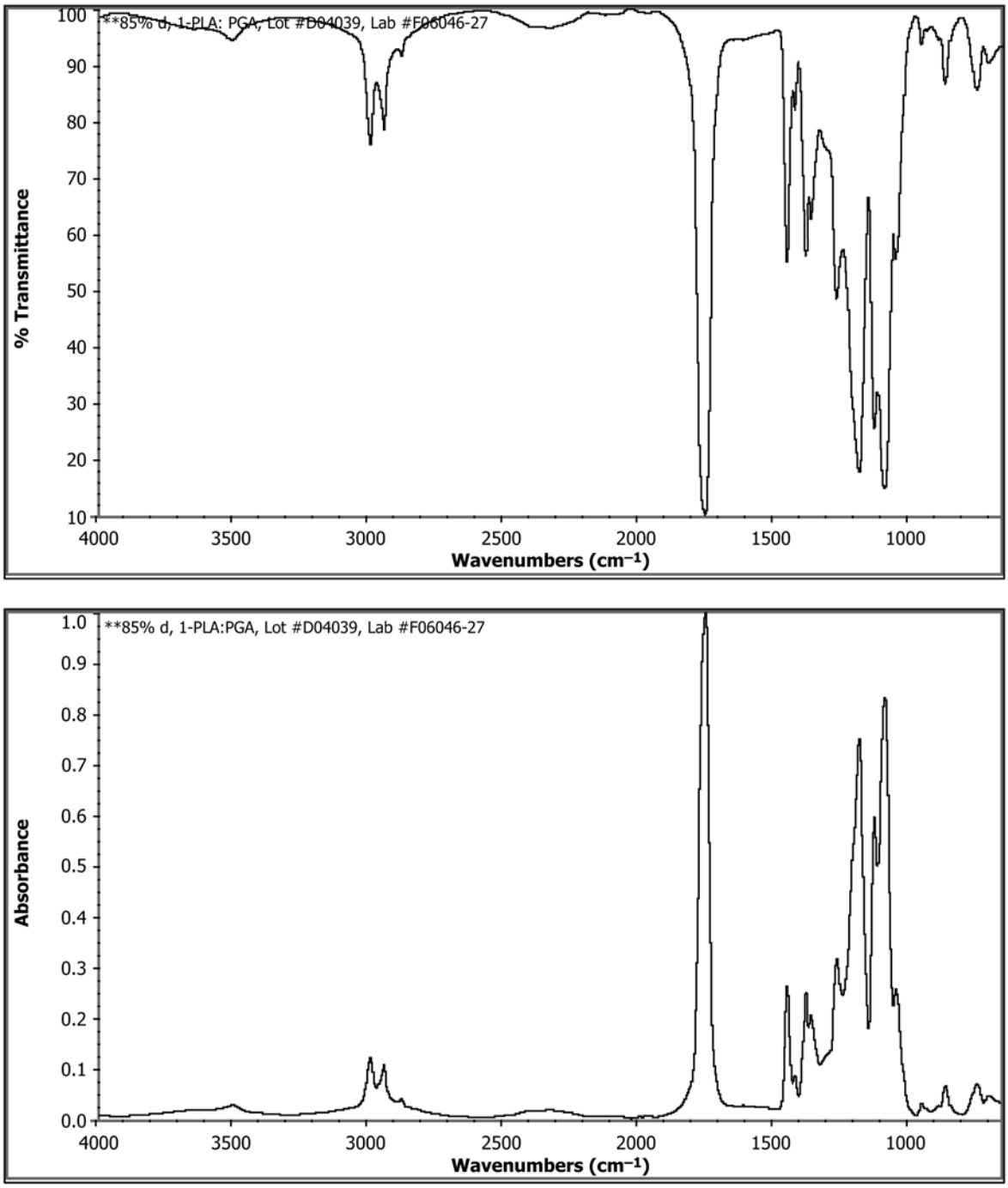
Example infrared spectra are alternative presentations of an amorphous 100 % DL-PLA homopolymer. (Spectra are courtesy of W. L. Gore & Associates, Inc., Flagstaff, AZ 86001, USA.)

FIG. 1 Poly(DL-lactide) Resin Infrared Spectra

where:

IV = inherent viscosity (at 30°C in dL/g),
t = efflux time in seconds for diluted solution,
t_o = 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.



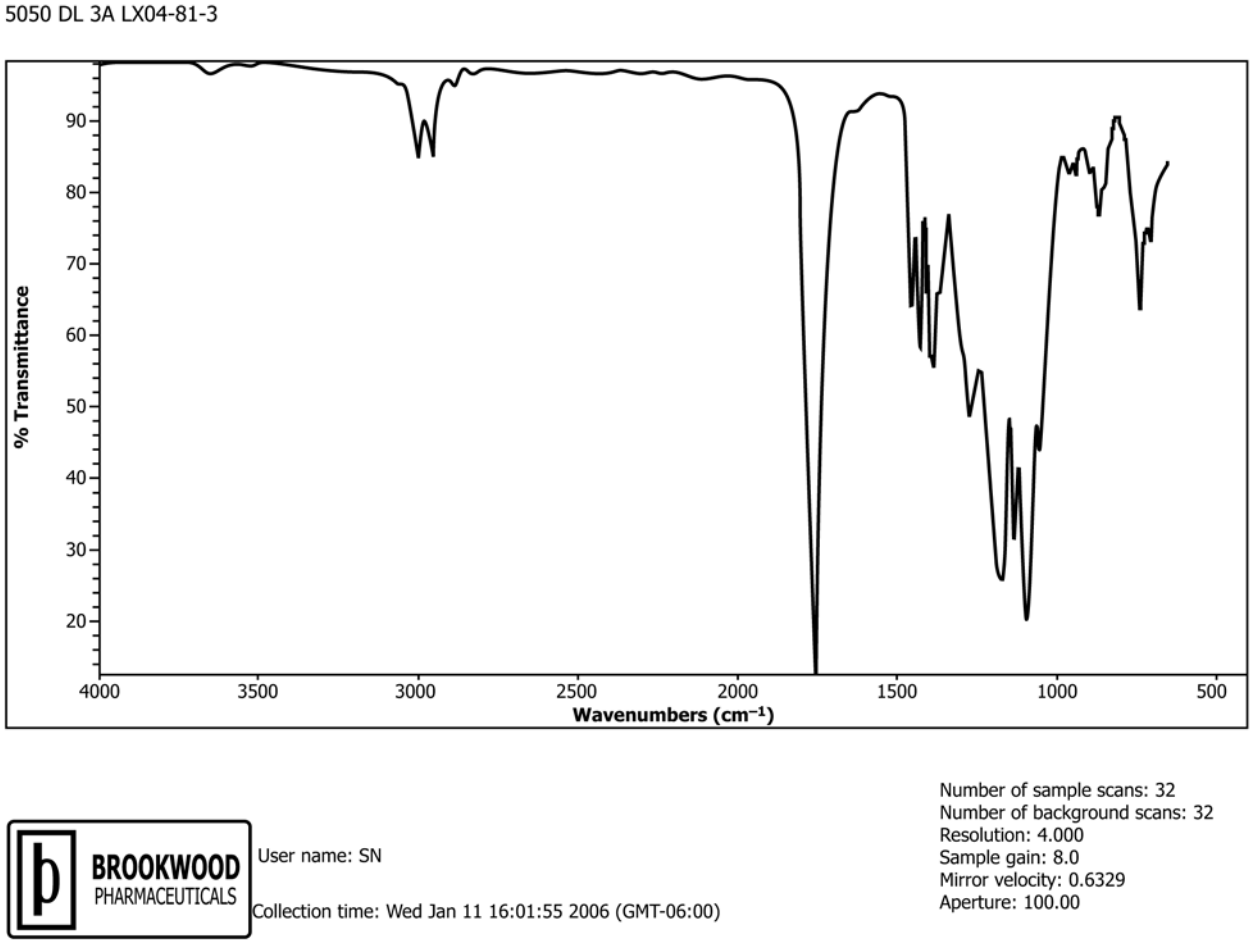
Example infrared spectra are alternative presentations of an amorphous 85% DL-PLA:15% PGA (mole ratio) copolymer. (Spectra are courtesy of W. L. Gore & Associates, Inc., Flagstaff, AZ 86001, USA.)

FIG. 2 Poly(lactide-co-glycolide) Resin Infrared Spectra

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 monomer content significantly less than 2 % to address processing or intended end-use requirements, or both (see Section S1—Biocompatibility).

5.5.2 Determine the mass fraction of residual monomer by gas chromatography, HPLC, ^{1}H-NMR spectroscopy (using deuterated chloroform, deuterated dichoromethane or other



Supplied example infrared spectrum of an amorphous 50 % DL-PLA:50 % PGA (mole ratio) copolymer is courtesy of Lakeshore Biomaterials, 756 Tom Martin Dr., Birmingham, AL 35211, USA.

FIG. 2 Poly(lactide-co-glycolide) Resin Infrared Spectra *(continued)*

substantially proton-free solvent able to fully solvate the specimen), or other suitably sensitive analytic method as agreed upon by the supplier and purchaser.

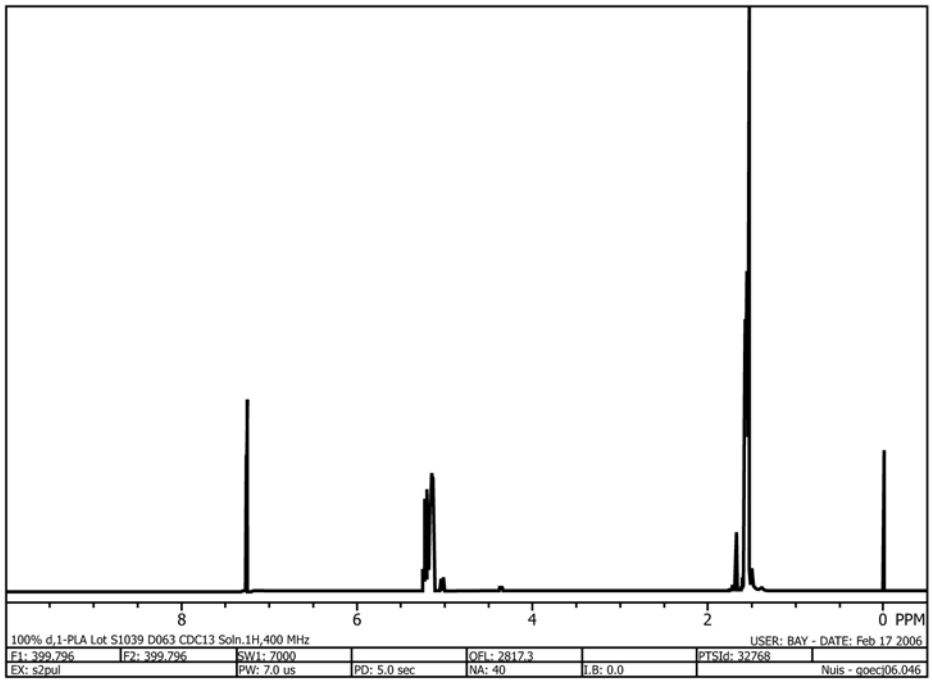
5.6 *Residual Solvents:*

5.6.1 If any solvent is utilized in any resin manufacturing or purification step, determine the 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. The detection limit for the chosen analytic method shall be adequate to assure 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 instead of a limit.

5.6.2 To minimize 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 has 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 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 the ICH HARMONISED GUIDELINE FOR ELEMENTAL IMPURITIES - Q3D.



Supplied example NMR spectrum of an amorphous 100 % DL-PLA homopolymer is courtesy of W. L. Gore & Associates, Inc., Flagstaff, AZ 86001, USA.

FIG. 3 Poly(DL-lactide) Nuclear Magnetic Resonance Spectrum

5.7.2 Determine the concentration of the respective Elemental Impurities within the absorbable polymer by utilizing a 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 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 assured to be maintained within the Parenteral Concentration - Individual Component Option limits, the resin "complies" with 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 <232> limits, the resin does not comply with the USP <232> ELEMENTAL IMPURITIES – LIMITS (except catalyst) and the concentration (in ppm, in accordance with USP <233> or equivalent) of each uncontrolled element is to be both monitored and reported.

5.7.3.1 The Elemental Impurities thresholds for the Individual Component Option of USP <232>, Table 3, provide specific elemental daily dosage limits for parenteral drug products. These daily Elemental Impurity limits (including those applied to catalyst concentrations) should be considered as conservative thresholds for informational purposes only when applied to absorbable implants. Proper application of these limits should consider the amount of polymer in the final implant product as well as its degradation and elemental elution rate into the surrounding tissue.

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

5.8 *Residual Catalyst:*

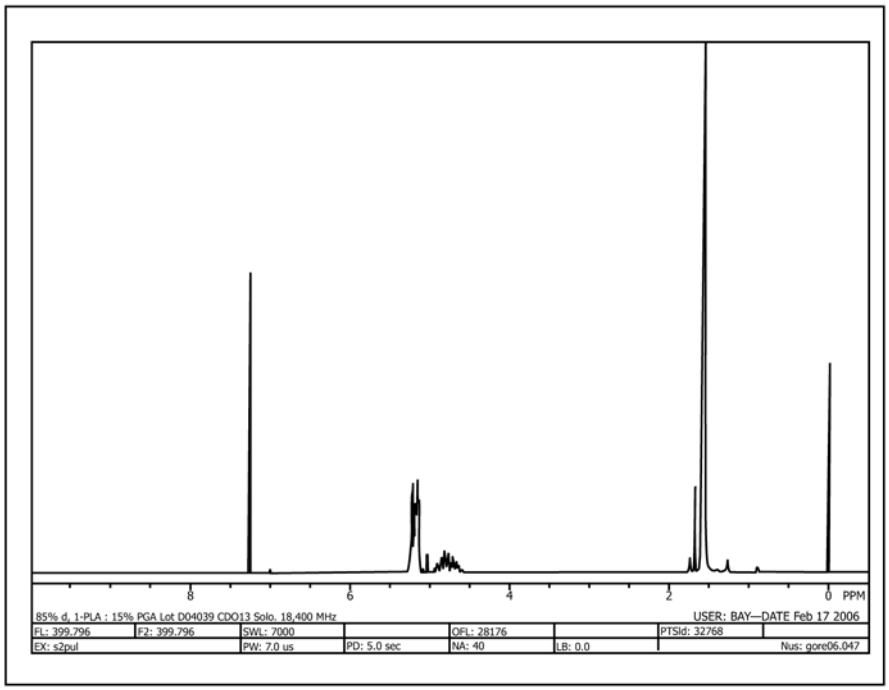
5.8.1 Determine the elemental concentration of residual catalyst as described in USP <233>. If the utilized catalyst is not measurable via USP <233>, suitable methods to both determine and report the catalyst residue shall be utilized.

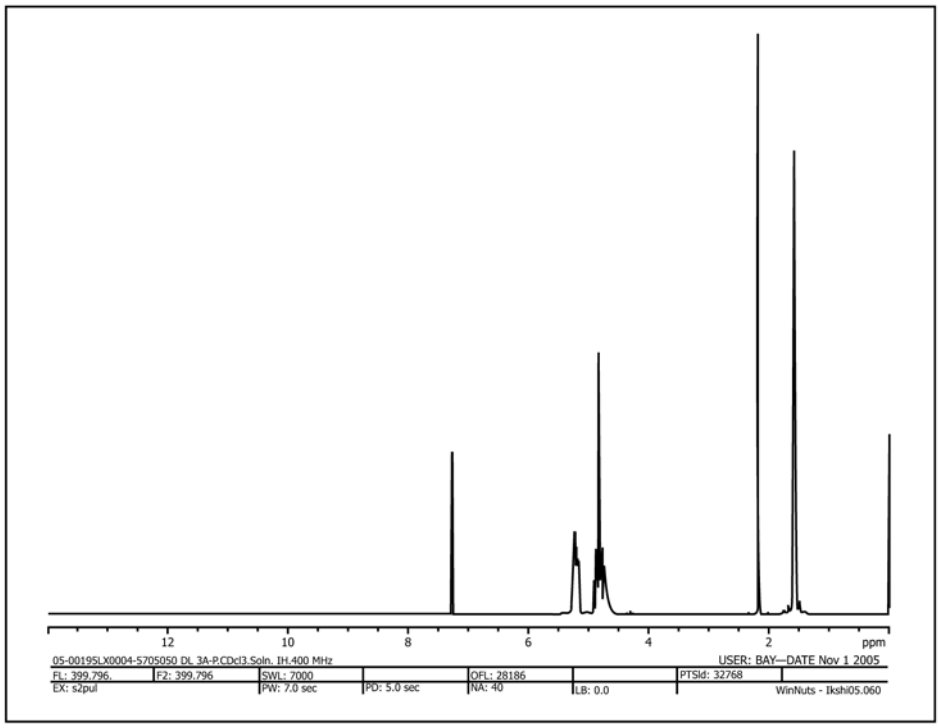
NOTE 4—The chemical nature and amount of residual catalyst can significantly affect both implant biocompatibility and polymer degradation during thermal processing. Since the resin supplier can provide the purchaser with accurate information regarding both the chemical nature and amount of added catalyst, reporting of actual added catalyst can be substituted for direct elemental testing.

5.9 *Residual Water (Optional):*

5.9.1 Using an analytic method agreed upon by the supplier and purchaser, ascertain that the amount of residual moisture (water) within the resin is less than or equal to 0.5 % by mass. Suitable methods include, but are not limited to, gravimetric and Karl Fisher titration methodologies—provided utilized sample quantities are adequate to assure a detection limit of 0.5 % or less.

NOTE 5—Residual water (moisture) can significantly affect polymer degradation during thermal processing. However, since polymers covered by this specification may be utilized in a wide variety of differing processes (which may or may not incorporate moisture control), resin moisture content may or may not be significant to a particular purchaser. Thus, this specification does not contain a moisture content requirement and direct testing for residual water is listed here as optional.





Supplied example NMR spectra of amorphous 85 % DL-PLA:15% PGA and 50 % DL-PLA:50 % PGA (mole ratio) copolymers are courtesy of W. L. Gore & Associates, Inc., Flagstaff, AZ 86001, USA.

FIG. 4 Poly(DL-lactide-co-glycolide) Nuclear Magnetic Resonance Spectra

6. Physical Properties

6.1 *Density*—Determine the density of the supplied resin in accordance with Test Method D1505 or other suitable method.

7. Performance Requirements

7.1 *Identification Requirements:*

7.1.1 Identity of amorphous poly(lactide) homopolymer or poly(lactide-co-glycolide) copolymer shall be confirmed through either an infrared, a ^{1}H-NMR spectrum (using deuterated chloroform, deuterated dichoromethane or other substantially proton-free solvent able to fully solvate the specimen), or a ^{13}C-NMR spectrum which exhibits major absorption bands

TABLE 1 Physical/Chemical Property Requirements for Virgin Amorphous Poly(lactide) and Poly(lactide-co-glycolide) 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 %[A] (by mass)	<1000 ppm	Report both for all solvent(s) utilized	≤0.5 % (by mass)[B]	Report compliance per USP <232>[C]	Report per USP <233>[D]	±3 % of target (by mole)	-2.5° to +2.5°

[A] Up to 3 % if deemed acceptable by purchaser (see 5.5.1).
[B] Utilizing a moisture determination method agreed upon by the supplier and the purchaser.
[C] See 5.7.3.
[D] See 5.8.1 and Note 4.

only at the wavelengths/chemical shifts that appear in a suitable reference spectrum.

7.1.2 The copolymer ratio of poly(lactide) to all non-lactide-based copolymeric components shall be determined either through a ^{1}H-NMR spectrum (using deuterated chloroform, deuterated dichoromethane, or other substantially proton-free solventable to fully solvate the specimen) or another suitably sensitive analytic method with resolution and specificity able to differentiate polymeric composition from residual monomer. The ratio of each respective copolymeric component shall be ±3 % in mole fraction of target. If utilized, this same ^{1}H-NMR spectrum may also provide the identification requirements of 7.1.1.

NOTE 6—NMR is unable to resolve between L-lactide, D-lactide, and DL-lactide stereoisomers.

7.2 *Molar Mass Requirements*—The finished resin product shall meet the specified molar mass requirements agreed upon between the supplier and purchaser as measured by inherent viscosity. Optional molar mass distribution criteria (as measured by the GPC methods described above) may also be specified and agreed upon between the resin supplier and device manufacturer.

7.3 *Physical/Chemical Property Requirements*—The virgin polymer shall have the chemical and physical properties listed in Table 1 as determined by the methods described above.

8. Dimensions, Mass, and Permissible Variations

8.1 Finished product resin may be supplied in pellet, granular, powder, flake or other suitable form, with requirements as agreed upon between the supplier and purchaser.

9. Sampling

9.1 Where applicable, the requirements of this specification shall be determined for each lot of virgin polymer utilizing sampling sizes and procedures described in Practice E1994 or an equivalent standard guidance.

10. Certification

10.1 A certificate of compliance or a certificate of analysis that, at minimum, contains the following information shall be supplied for each shipment:

10.1.1 Supplier identification (including address and phone contact numbers),

10.1.2 Resin lot number,

10.1.3 Date of certification (include purchaser specification, if applicable),

10.1.4 Chemical description of the polymer (including stereoisomeric composition and, if appropriate, the targeted copolymer ratio designated specifically by mass or by mole),

10.1.5 Applicable CAS registry number,

10.1.6 Experimentally determined copolymer ratio (if a copolymer, with results designated by mass or by mole),

10.1.7 Inherent viscosity (in dL/g; with solvent, temperature, and analyte concentration in solution); if requested by the purchaser, inherent viscosity (30°C extrapolated) is also reported if actual experimental value was determined at 25°C,

10.1.8 Residual monomer content (combined total in mass %),

10.1.9 *Elemental Impurities—Limits (Except Catalyst):*

10.1.9.1 Report either "complies" or list element(s) and concentration(s).

10.1.10 *Residual Catalyst, ppm:*

10.1.10.1 Report element(s) and concentration(s).

10.1.11 Residual solvent(s), if any, and applied ICH concentration limit(s).

NOTE 7—Relevant properties described herein as "optional" and measured as agreed upon between the purchaser and supplier may be listed on the Certificate of Analysis or Certificate of Compliance.

11. Packaging and Package Marking

11.1 Packaging material shall be of such composition that it provides an effective barrier to the entry of moisture.

11.2 Each individually supplied product packaging shall possess a label that contains the following information:

11.2.1 Supplier identification,

11.2.2 A chemical description of the polymer (including, if appropriate, the targeted copolymer ratio designated specifically by mass or by mole),

11.2.3 Resin lot number,

11.2.4 Net mass of contents, and

11.2.5 Inherent viscosity (as analyzed, in dL/g).

12. Guidance for Manufacturing Control and Quality Assurance

12.1 Acceptable levels of manufacturing control are highly desirable and may apply to the manufacture of the resin. Good Manufacturing Practice guidelines for achieving acceptable levels of manufacturing quality control may be found in:

12.1.1 21 CFR 820 Code of Federal Regulations, Title 21, Part 820, Quality System Regulation.

12.1.2 ANSI/ISO/ASQ Q9000—Provides fundamentals for quality management systems as described in the ISO 9000

family (informative); and specifies quality management terms and their definitions (normative).

12.1.3 ANSI/ISO/ASQ Q9001—Presents requirements for a quality management system. The application of this specification can be used by an organization to demonstrate its capability to meet customer requirements for products and/or services, and for assessment of that capability by internal and external parties.

12.1.4 ANSI/ISO/ASQ Q13485—Presents requirements for a quality management system specific to medical device design and manufacturing. The application of this specification can be used by an organization to demonstrate its capability to meet customer requirements for products and/or services, and for assessment of that capability by internal and external parties.

13. Keywords

13.1 poly (DL-lactic acid); poly (DL-lactide); PDLLA; PGA-:PLA; PLA; PLA:PGA; PLGA; polyglycolic:lactic acid; poly(glycolide-co-lactide); poly(glycolide:lactide); poly(lactic acid); polylactic:glycolic acid; poly(lactide); poly(lactide-co-glycolide); poly(lactide:glycolide); polylactide

SUPPLEMENTARY REQUIREMENTS

S1. Biocompatibility

S1.1 Due to the potential for an increase in local acidity as a result of either residual monomer or the normal hydrolytic degradation process, suitability of these materials for human implantation will be dependent on the implant's form and specific clinical application. For example, with respect to implant surface-to-volume ratio, the same level of residual monomer appropriate for braided sutures, open porous structures, or thin barrier films utilized in highly perfused soft tissue may not be acceptable for larger solid devices intended for bony site applications. Biological tests appropriate for the specific site, such as those recommended in ISO 10993 and in Practice F748, may be used as a guideline.

S1.2 The biocompatibility of powders, resins, test samples, or devices fabricated from these polymers can optionally be determined in accordance with ISO 10993-1, Practice F748, or otherwise as agreed upon between the supplier and the device manufacturer. Determination of an implant's biocompatibility is a biological risk assessment process that is dependent on the intended application and is established through a biological evaluation of the finished product after completion of all processing steps, including sterilization.

S1.3 No known surgical implant material has ever been shown to be completely free of adverse reactions in the human body. However, long-term clinical experience with specific compositions and formulations of the material class referred to in this specification has shown that an acceptable level of biological response can be expected if the material is used in appropriate applications.

APPENDIXES

(Nonmandatory Information)

X1. NOMENCLATURE

X1.1 Poly(glycolide) is commonly abbreviated as PGA for poly(glycolic acid), referring to the chemical byproduct to which it degrades after hydrolysis. PGA contains no chiral carbon and therefore has no stereoisomeric forms that require identification. Poly(lactide) is commonly abbreviated as PLA for poly(lactic acid), referring to the chemical byproduct to which it degrades after hydrolysis. The PLA repeating unit does contain a chiral carbon and therefore has two stereoisomeric forms that require appropriate identification within the specification. Since lactate, the conjugate base of lactic acid, is able to be generated through anaerobic glycolysis of sugars (such as glucose, fructose, and sucrose), its stereoisomeric descriptors follow the D and L nomenclature system generated by Emil Fisher in 1891 for carbohydrates. This system designates a monosaccharide as either D- or L- (using small capital letters) based on configuration matching of its highest numbered chiral carbon to either D-glyceraldehyde [also (*R*)-glyceraldehyde] or L-glyceraldehyde [also (*S*)-glyceraldehyde]. Accordingly, racemic (equimolar) mixtures of two stereoisomers are abbreviated with a DL- or a (*R,S*) designation. Thereby,within the medical products industry and its literature, abbreviations for the lactide are typically in the form of L-PLA or DL-PLA. Of additional note is that this D and L system is intended to convey absolute configuration and differs from the terms levorotatory and dextrorotatory, which indicate the empirically determined rotation of plane polarized light to the left [abbr.: *l*- or (–)] and right [abbr.: *d*- or (+)], respectively.

X1.2 Amorphous polylactide can be synthesized from two distinctly different methods, each dependent on the selected monomeric source. One approach to produce DL-PLA-based polymers and copolymers is to use *meso* -lactide, which

contains both D and L stereoisomers within a single monomeric lactide dimer. An alternate approach is to copolymerize racemic equimolar quantities of both D-lactide and L-lactide stereoisomeric monomers to produce the DL-PLA-based polymers and copolymers. Exclusive synthetic use of *meso*-lactide assures full stereoisomeric mixing and generates an atactic polymer that precludes any potential for crystallization of extended L-lactide or D-lactide chain segments. Syntheses of syndiotactic PLA derived from racemic mixtures of both D-lactide and L-lactide stereoisomeric monomers can be amorphous if cumulative monomer and copolymerization mixing is sufficient to reliably generate same stereoisomeric segment lengths that are sufficiently short to prevent crystallization. Adequate mixing during copolymerization with glycolide is also important to assure segment lengths that are sufficiently short to prevent crystallization of PGA, either from solution or after cooling from the melt.

X2. RATIONALE

X2.1 This specification is written for virgin amorphous poly(lactide)-based resins and is not intended to be applied to objects (for example, test samples or devices) fabricated from PLA or PLA:PGA. The properties of objects fabricated from amorphous poly(lactide) resins, such as mechanical properties, are dependent upon the processing conditions used during fabrication and thus fall outside of the scope of this resin standard. Properties in this specification are therefore specified only for amorphous poly(lactide)-based resin and not for its fabricated form. There are several ASTM and ISO standards listed in Guide F2902 which can be used to determine the chemical, physical, mechanical, and biological properties of devices or test samples fabricated from these resins.

X2.2 Amorphous poly(lactide)-based resin may be synthesized with many different molar mass ranges and distributions. Each such system will possess unique molar mass-dependent properties. Therefore certain physical, mechanical, and thermal properties (for example, glass transition, melt temperatures, and tensile properties) are not specified in this document.

X2.3 Most amorphous poly(lactide)-based resin suppliers will, upon request, provide analyses relating to bioburden and/or pyrogens. Bioburden is a measure of the number of viable cell colonies (aerobic, anaerobic, and spore cells) per gram of resin material. Pyrogen content is a measure of the presence of bacterial endotoxins which is commonly measured by the Limulus Amebocyte Lysate test (see 2.4). Because these properties may be significantly influenced by exposure of the resin to any nonsterile environment, such properties are not required in this materials standard.

X2.3.1 While it is obviously ideal to have zero foreign particles within any bioabsorbable implant material, under practical processing conditions it must be expected that processing-related particles of foreign matter may be present to some degree. Particulate amounts may be quantified through various means, such as utilization of USP <788> Particulate Matter in Injections. Unfortunately, at this time, there are no studies dealing with typical foreign particle levels in this resin material or their effect upon resin properties. Such a specification may be established in the future as information regarding this parameter is developed by methods such as round-robin use of this specification for selected samples of PLA-based resin from various commercial sources.

X2.4 Chemical identification with comparison to a known standard (in accordance with 5.2 and 7.1.2) requires either an infrared or a NMR analysis, both of which provide broad chemical characterization of the analyte's organic composition. Utilization of such broad characterization methods provides the analytic ability to readily identify either a differing polymer (including incorrect copolymer ratios) or the correct polymer containing substantial levels of non-specific organic contamination. Alternative analytical methods may be utilized specifically to quantify the copolymer ratio, providing sensitivity is adequate to assure compliance with specification requirements and both resolution and specificity are adequate to exclude residual monomer.

X2.5 *Elemental Impurities Limits*—The USP <231> "Heavy Metals as Lead" method was obsoleted on Dec. 1, 2017 and has been replaced with USP <233>, which outlines acceptable analytical methods for determining the concentrations of individual elemental impurities. USP <232> describes a risk-based approach to setting limits on elemental impurities for pharmaceuticals. While medical devices are not within the scope of USP <232>, the limits set for parenteral drugs can be applied to absorbable materials by estimating the release rate of elemental impurities based on their concentrations and the degradation rate of the device. If the concentration of an elemental impurity within the resin complies with the Parenteral Concentration - Individual Component Option limits of USP <232> no risk analysis is needed.

The term "Heavy Metals" has been dropped in favor of "Elemental Impurities" in keeping with the ICH harmonized guideline on elemental impurities, Q3D. The term "Heavy Metals" is imprecise and there is confusion as to exactly which elements are included. Furthermore, the "Heavy Metals as Lead" method is based on the reaction of various metal cations with sulfide and, therefore, cannot distinguish between those elements. It is also a limit test, meaning that it can only determine whether the total concentration of metals is less than or greater than a pre-set value, which is assumed to be lead. In contrast, the ICH harmonized USP guidance lists 24 elements of interest, which are categorized according to their toxicities, with individual limit values varying accordingly, The methods outlined in USP <233> are quantitative and highly sensitive, so the concentration of each element of interest can be determined. This provides more detailed information that allows a more robust risk analysis with fewer conservative assumptions.

X2.6 *Residual Catalyst*—The catalysts used in the synthesis of many absorbable polymers are compounds based on metals that are included in the elements of interest listed in USP <232> and the ICH-Q3D guidelines. The most common catalysts for the polymers covered by this specification are based on tin (Sn).

Catalysts are intentionally added in quantities that will often exceed the limit set for the Individual Component Option of USP <232>, Table 3. Therefore a risk analysis may be required to determine the allowable limit of residual catalyst, based on the size of the device, its degradation rate, and the intended application. It is notable that in previous versions of this specification a limit of 150 ppm of Sn was used, and many successful medical devices have been fabricated from polymers with residual catalyst concentrations close to 150 ppm. However, any risk analysis needs to be within the context of the product's intended application and should consider the element itself, its oxidation state (if applicable), the element's concentration within the polymer, as well as the product's total amount of absorbable polymer and its anticipated rate of degradation.