Designation: F2313 – 10

Standard Specification for Poly(glycolide) and Poly(glycolide-co-lactide) Resins for Surgical Implants with Mole Fractions Greater Than or Equal to 70 % Glycolide[1]

This standard is issued under the fixed designation F2313; 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 both virgin poly(glycolide) homopolymer and poly(glycolide-co-lactide) copolymer resins intended for use in surgical implants. The poly(glycolide-co-lactide) copolymers covered by this specification possess nominal mole fractions greater than or equal to 70 % glycolide (65.3 % in mass fraction). This specification is also 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.

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.

1.3 This specification is specifically not applicable to amorphous poly(lactide-co-glycolide) or poly(lactide)-based resins able to be fully solvated at 30°C by either methylene chloride (dichloromethane) or chloroform (trichloromethane), which are covered in Specification F2579 and typically possess molar glycolide levels of ~50 % or less. 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.

1.4 This specification addresses material characteristics of both virgin poly(glycolide) and poly(>70 % glycolide-co-lactide) 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, etc.) 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 and health practices and determine the applicability of regulatory limitations prior to use.*

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

D5296 Test Method for Molecular Weight Averages and Molecular Weight Distribution of Polystyrene by High Performance Size-Exclusion Chromatography

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

E386 Practice for Data Presentation Relating to High-Resolution Nuclear Magnetic Resonance (NMR) Spectroscopy

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

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[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.

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
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
F2579 Specification for Amorphous Poly(lactide) and Poly(lactide-co-glycolide) Resins for Surgical Implants

2.2 *ANSI Standards:*[3]

ANSI/ISO/ASQ Q9000 Quality Management Systems; Fundamentals and Vocabulary
ANSI/ISO/ASQ Q9001 Quality Management Systems; Requirements

2.3 *ISO Standards:*[3]

ISO 31–8 Physical Chemistry and Molecular Physics—Part 8: Quantities and Units
ISO 10993 Biological Evaluation of Medical Devices
ISO 11357 Plastics—Differential Scanning Calorimetry (DSC)

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

USP30/NF25 United States Pharmacopeia (USP), May 2, 2007

2.5 *Other Documents/Websites:*

ICH Q3C(R3) International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Quality Guideline: Impurities: Residual Solvents[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]

[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/LOB/media/MEDIA423.pdf.

[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.

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 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 poly(glycolide) polymers covered by this specification shall be composed of glycolide or a combination of glycolide or lactide where the lactide content does not exceed 30 % mole fraction (34.7 % by 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.

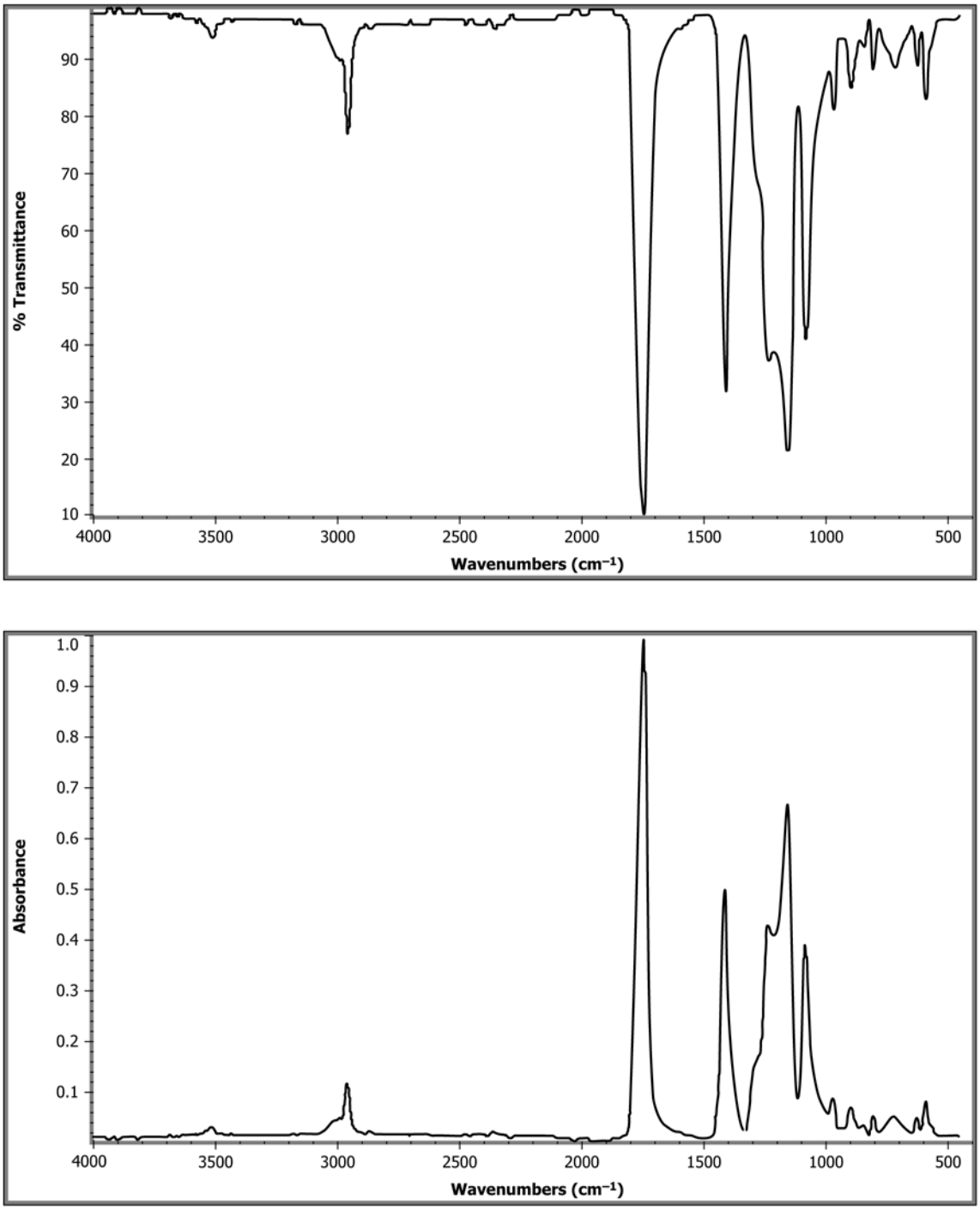
5.2.2 *Infrared Identification:*

5.2.2.1 Identity of either poly(glycolide) homopolymer or poly(glycolide-co-lactide) 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 practices similar to those described in Practice E1252. Typical infrared transmission and absorbance reference spectra are presented for PGA homopolymer in Fig. 1 and 90 % PGA:10 % L-PLA copolymer in Fig. 2. While poly(glycolide-co-lactide) 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).

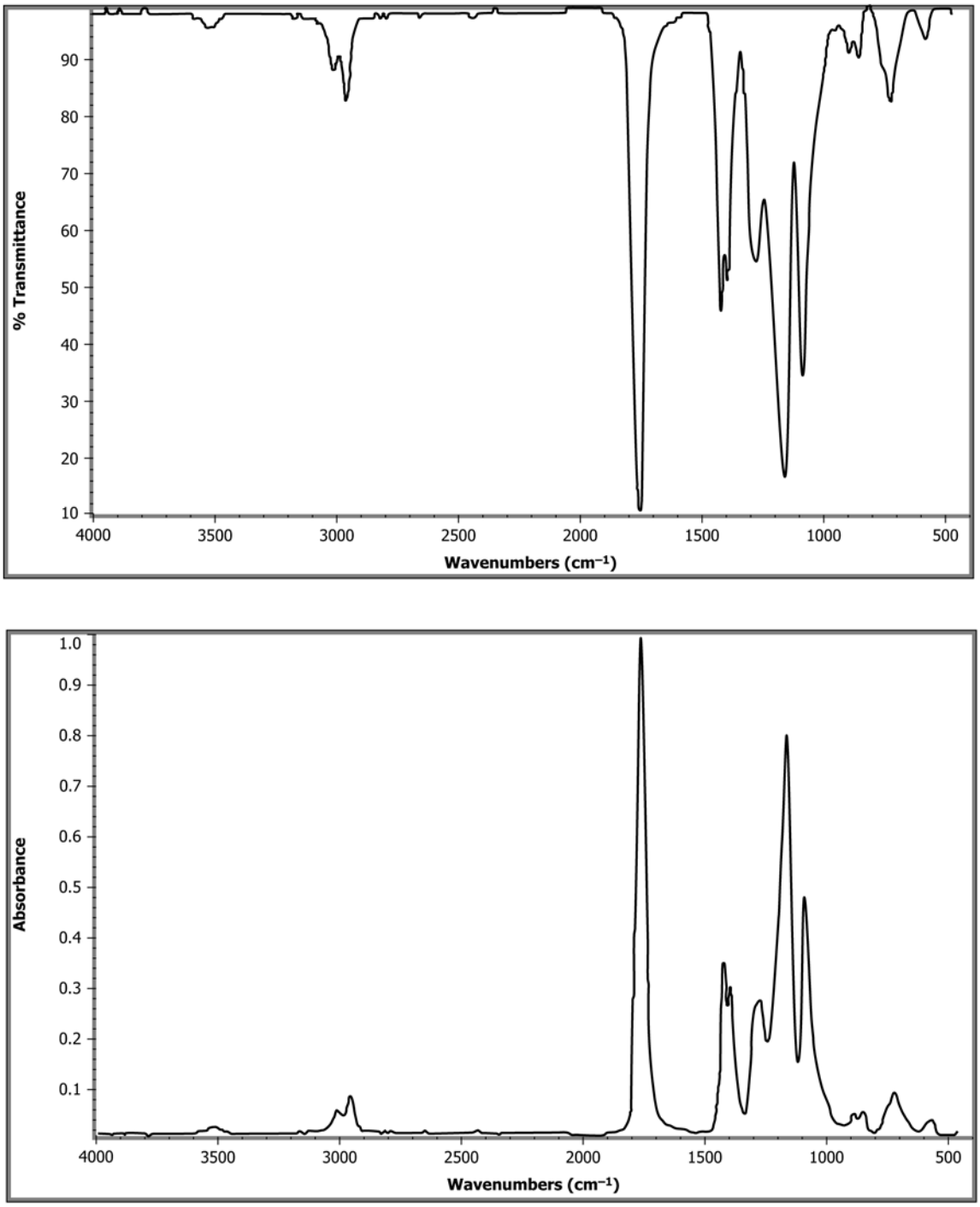
5.2.3 *Proton Nuclear Magnetic Resonance (^{1}H-NMR) Identification:*

5.2.3.1 Identity of either poly(glycolide) homopolymer or poly(glycolide-co-lactide) 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 hexafluoroisopropanol (D-HFIP) or other substantially proton-free solvent able to fully solvate the



NOTE 1—Supplied example infra-red spectrum is of "Dexon Medical Suture (beige)" as acquired from the Hummel Polymer Library, available from: Thermo Nicolet Corporation, 5225 Verona Road, Madison, WI 53711-4495, USA.

FIG. 1 Poly(glycolide) Resin Infrared Spectrum



NOTE 1—Supplied example infra-red spectrum is of "Vicryl Medical Suture (violet)" as acquired from the Hummel Polymer Library, available from: Thermo Nicolet Corporation, 5225 Verona Road, Madison, WI 53711-4495, USA.

FIG. 2 Poly(90 % glycolide-co-10 % lactide) Resin Infrared Spectrum

TABLE 1 Physical/Chemical Property Requirements for Virgin Poly(glycolide) and Poly(glycolide-co-lactide) 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 (%)	Heavy Metals, (ppm as Pb)	(Optional) Residual Catalyst (in ppm)	Copolymer Ratio
Requirement	≤2.0 % (by mass)	<1000 ppm	Report both for all solvent(s) utilized	≤0.5 % (by mass)[A]	≤10 ppm (minus Sn)	≤100 ppm Sn	±3 % of target (by mole)

[A] Utilizing a moisture determination method agreed upon by the supplier and the purchaser.

specimen without inducing competing spectral bands. Analysis shall be conducted using practices similar to those described in Practice E386.

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(glycolide) homopolymer or poly(glycolide-co-lactide) 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 practices similar to those described in Practice E386.

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 *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 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 the general procedure described in Test Method D5296, but using hexafluoroisopropanol (HFIP) solvent and poly methylmethacrylate (PMMA) 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.

5.3.1.1 Determine the inherent viscosity of the polymer either in hexafluoroisopropanol (HFIP) or hexafluoroacetone sesquihydrate (HFAS) 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. 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.

5.3.1.2 Inherent viscosity is determined utilizing the following:

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

or

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

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*).

5.3.1.3 Resin concentration shall be 0.5 % *w/v* or less, with resin analyte concentrations of 0.1 % *w/v* (that is, 0.001 g/mL or 1 mg/mL) recommended. 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 less than or equal to 2.0 % in mass fraction.

5.4.1.1 Determine the mass fraction of residual monomer by gas chromatography, HPLC, ^{1}H-NMR spectroscopy (using D-HFIP 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(R3). The detection limit for the chosen analytic method must 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 lieu of a limit.

5.5.2 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 carries the effect of allowing ICH QC3 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).

5.6 *Heavy Metals:*

5.6.1 Determine residual Heavy Metals per Method II, Chapter 231 of U. S. Pharmacopeia (USP30/NF25).

5.6.2 Heavy metals generally refers to divalent cations of the elements cadmium (Cd), copper (Cu), mercury (Hg), and lead (Pb), to the trivalent cations of antimony (Sb), arsenic (As), and bismuth (Bi), and to tetravalent (stannic) tin (Sn^{4+}) that form complexes with sulfide under slightly acidic conditions.[8] Since stannous tin (Sn^{2+}) can also form tin (II) sulfide and therefore can potentially influence test results, the excess amount ascertained by alternative analytic means to be directly attributable to both stannic and stannous tin may be ignored, provided that the cumulative lead (Pb) equivalent total of the remaining listed heavy metals elements determined through the same alternative analytic means (see discussion and calculations in X2.5) remains below a 10 ppm as lead (Pb) limit.

5.7 *Residual Catalyst (Optional):*

5.7.1 Determine the amount of residual tin (Sn) and each of the above listed heavy metal elements 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.

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, direct testing for residual catalyst is listed here as optional.

5.8 *Residual Water (Optional):*

5.8.1 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.

[8] See discussion regarding Heavy Metals General Test in *Reagent Chemcials* (10th Edition), American Chemical Society, Analytical Inorganic Subcommittee, Minutes–October 5, 2005; available online at http://pubs.acs.org/reagents/cominfo/minutes.html.

6. Physical Properties

6.1 *Density:*

6.1.1 Determine the density of the supplied resin in accordance with Test Method D1505.

6.2 *Thermal/Crystalline Characteristics (Optional):*

6.2.1 Glass transition temperatures, melting temperatures, and crystallinity may affect the ultimate mechanical properties of a semi-crystalline polymer-based finished product, such as those fabricated from polyglycolide. Measurement of these thermal properties within the base resin may be appropriate to assure consistency in finished product mechanical properties and to identify lot-to-lot variations.

6.2.2 No specific standard method for DSC evaluation of polyglycolide based resins currently exists. Methodology that may be suitable for DSC measurement of the glass transition, melting temperature, and crystallinity of PGA resin include Test Methods D3418, E793, E794, E1356, Terminologies E473 and E1142, and Practices E967 and E968. Other potentially relevant standards include one or more parts of the ISO 11357 series. Selection of a particular test methodology and a minimum crystallinity may be agreed upon by the supplier and the purchaser. Crystallinity, as determined through quantification of the heat of fusion (also known as melt enthalpy) peak, preferentially should be expressed in units of Joules per gram (J/g). Obtained results may be also expressed as percentage (%) crystallinity, provided both the test report and relevant resin specification provide an explicit citation to an identifiable 100 % crystallinity reference for PGA, such as one of the following:

6.2.2.1 Grinde and Gupta,[9] which reported a calculated theoretical 100 % crystalline sample of PGA to be 49.34 cal/g (206.4 J/g).

6.2.2.2 Cohn, Younes, and Marom,[10] which reported the heat of fusion of an infinite PGA crystal to be 139 J/g.

6.2.2.3 Nakafuku and Yoshimura,[11] which reported PGA heat of fusion to be 183.2 J/g.

6.2.2.4 Chujo, Kobayashi, Suzuki, Tokuhara, and Tanabe,[12] which calculated melting point depression to be 180.4 J/g from glycolide-lactide copolymerization and 202.1 J/g from glycolide-1,3 dioxolane copolymerization.

NOTE 6—Crystallinity may be alternatively determined by X-ray diffraction methods.

7. Performance Requirements

7.1 *Identification Requirements:*

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

[9] Grinde, R. M., and Gupta, R. K., "*in vitro* Chemical Degradation of Poly(Glycolic Acid) Pellets and Fibers," *J. App. Poly. Sci*., Vol 33, 1987, p. 2411.

[10] Cohn, D., Younes, H., and Marom, G., *Polymer*, Vol 28, 1987, pp. 2018–2022.

[11] Nakafuku, C., and Yoshimura, H., "Melting Parameters of Poly(glycolic acid)," *Polymer*, Vol 45, No. 11, 2004, pp. 3583–3585.

[12] Chujo, K., Kobayashi, H., Suzuki, J., Tokuhara, S., and Tanabe, M., *Makromol Chem*., Vol 100, 1967, pp. 262–266.

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

7.1.2 The copolymer ratio of glycolide to all non-glycolide-based copolymeric components must be determined either through a ^{1}H-NMR spectrum (using D-HFIP or other substantially proton-free solvent able 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 7—NMR is unable to resolve between L-lactide, D-lactide, and DL-lactide stereoisomers.

7.2 *Molar Mass Requirements:*

7.2.1 The finished resin product must meet the specified molar mass requirements agreed upon between the supplier and purchaser as measured by inherent viscosity. Optional molar mass distribution criteria may also be specified and agreed upon as measured by the GPC methods described above.

7.3 *Physical/Chemical Property Requirements:*

7.3.1 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, 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) shall also be reported if the actual experimental value was determined at 25°C,

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

10.1.9 Heavy metals (pass or fail, with applicable limit specified), and

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

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,

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

11.2.6 Final packaging date.

12. Guidance for Manufacturing Control and Quality Assurance

12.1 Acceptable levels of manufacturing control are highly desirable and may apply to 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,

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 standard 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(glycolic acid); poly(glycolide); PGA; poly(glycolide:lactide); poly(glycolide-co-lactide); PLA; PGA: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 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 stereisomeric descriptors follow the D and L nomenclature system generated by Emil Fiser 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 alternative 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 PGA or PGA-:PLA resin and is not intended to be applied to objects (for example, test samples or devices) fabricated from PGA or PGA:PLA. The properties of objects fabricated from PGA or PGA:PLA 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 poly(glycolide)-based resin and not for its fabricated form. Several potentially applicable ASTM standards are listed in Section 2 (Referenced Documents) may be followed to determine fabricated-form properties for devices and test samples fabricated from these resins.

X2.2 PGA or PGA:PLA 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 poly(glycolide)-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.

X2.4 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 USP30/NF25 <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 standard for selected samples of poly(glycolide)-based resin from various commercial sources.

X2.5 Chemical identification with comparison to a known standard (per 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.

X2.6 USP30/NF25 Heavy Metals <231> is a limit test that complexes numerous cationic metals with the sulfide (S^{2-}) anion, which imparts a coloration that is visually compared with an appropriate known concentration of lead standard solution. While divalent lead is the specific cation utilized for sulfide complex quantification, coloration resulting from complexes with other metallic cations is intentional and is directly compared with the same lead standard solution. Since the specified test conditions of this USP method define cationic sensitivity to sulfide coloration, no adjustment of non-lead cations for the their sulfide sensitivity is needed. However, correction to a lead equivalent concentration is necessary if individual non-lead metal concentrations are determined independently, as is typically the case when employing AA or ICP techniques.

X2.6.1 Assuming that all listed cations are ionically equivalent to divalent lead in their ability to create a sulfide color complex, adjustments of resin sample concentrations to compensate for differences in atomic mass and oxidation state may be made using the following formula:

$$\begin{matrix}\text{mg/kg}\\ \text{of metal}\\ \text{in sample}\end{matrix} \times \frac{\text{Atomic mass of Pb}}{\text{Atomic mass of metal}} \times \frac{^{+}\text{ charge metal}}{2^{+}\text{ charge Pb}} = \text{ppm as Pb} \quad \text{(X2.1)}$$

TABLE X2.1 Lead (Pb) Equivalent Concentrations for Heavy Metals Determined through Non-USP Methods

Metal	Symbol	Metal Sulfide Oxidation State (+ charge)	Element Atomic Mass (mg/mmol)	Pb Equivalent (ppm)
Antimony	Sb	3	121.75	2.6
Arsenic	As	3	74.9	4.1
Bismuth	Bi	3	209.0	1.5
Cadmium	Cd	2	112.4	1.8
Copper	Cu	2	63.6	3.3
Mercury	Hg	2	200.6	1.0
Lead	Pb	2	207.2	1.0

X2.6.2 Table X2.1 utilizes the above calculation to provide the calculated Pb equivalent for each of the cations listed in 5.6.2 as being responsive to Heavy Metals complexation.