Designation: F2313 – 18

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-colactide) 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, 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 Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

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

D2857 Practice for Dilute Solution Viscosity of Polymers

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

D5296 Test Method for Molecular Weight Averages and Molecular Weight Distribution of Polystyrene by High

[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.

Current edition approved Dec. 15, 2018. Published February 2019. Originally approved in 2003. Last previous edition approved in 2010 as F2313 – 10. DOI: 10.1520/F2313-18.

[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.

Performance Size-Exclusion Chromatography
D4603 Test Method for Determining Inherent Viscosity of Poly(Ethylene Terephthalate) (PET) by Glass Capillary Viscometer
E473 Terminology Relating to Thermal Analysis and Rheology
E793 Test Method for Enthalpies of Fusion and Crystallization by Differential Scanning Calorimetry
E794 Test Method for Melting And Crystallization Temperatures By Thermal Analysis
E967 Test Method for Temperature Calibration of Differential Scanning Calorimeters and Differential Thermal Analyzers
E968 Practice for Heat Flow Calibration of Differential Scanning Calorimeters
E1142 Terminology Relating to Thermophysical Properties
E1252 Practice for General Techniques for Obtaining Infrared Spectra for Qualitative Analysis
E1356 Test Method for Assignment of the Glass Transition Temperatures by Differential Scanning Calorimetry
E1994 Practice for Use of Process Oriented AOQL and LTPD Sampling Plans
E2977 Practice for Measuring and Reporting Performance of Fourier-Transform Nuclear Magnetic Resonance (FT-NMR) Spectrometers for Liquid Samples
F748 Practice for Selecting Generic Biological Test Methods for Materials and Devices
F1925 Specification for Semi-Crystalline Poly(lactide) Polymer and Copolymer Resins for Surgical Implants
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:*[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 11357 Plastics—Differential Scanning Calorimetry (DSC)
ISO 80000-9 Quantities and units -- Part 9: Physical chemistry and molecular physics

2.4 *U. S. Pharmacopeia (USP) Standards:*[4]
USP 232 United States Pharmacopeia: Elemental Impurities – Limits
USP 233 United States Pharmacopeia: Elemental Impurities – Procedure
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, 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:*

[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.

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 methods 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 specimen without inducing competing spectral bands. Analysis shall be conducted using methods similar to those described in Practice E2977.

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 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 *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 880000-9], 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.

5.3.1 The molar mass of the virgin polymer shall be indicated by inherent viscosity (IV) in dilute solution. In addition to (but not in place of) inherent viscosity, 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.

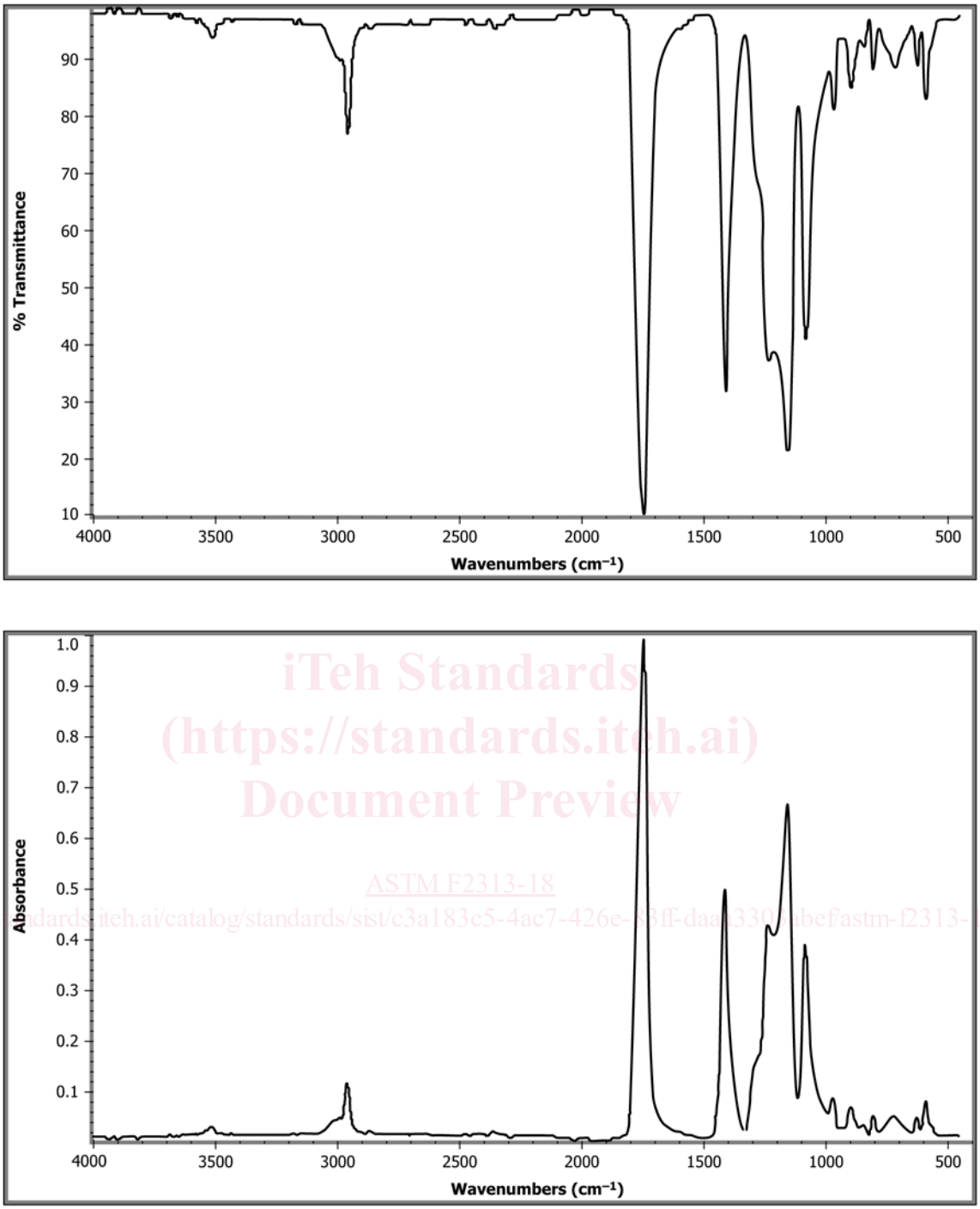
5.4 *Residual Monomer:*

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.

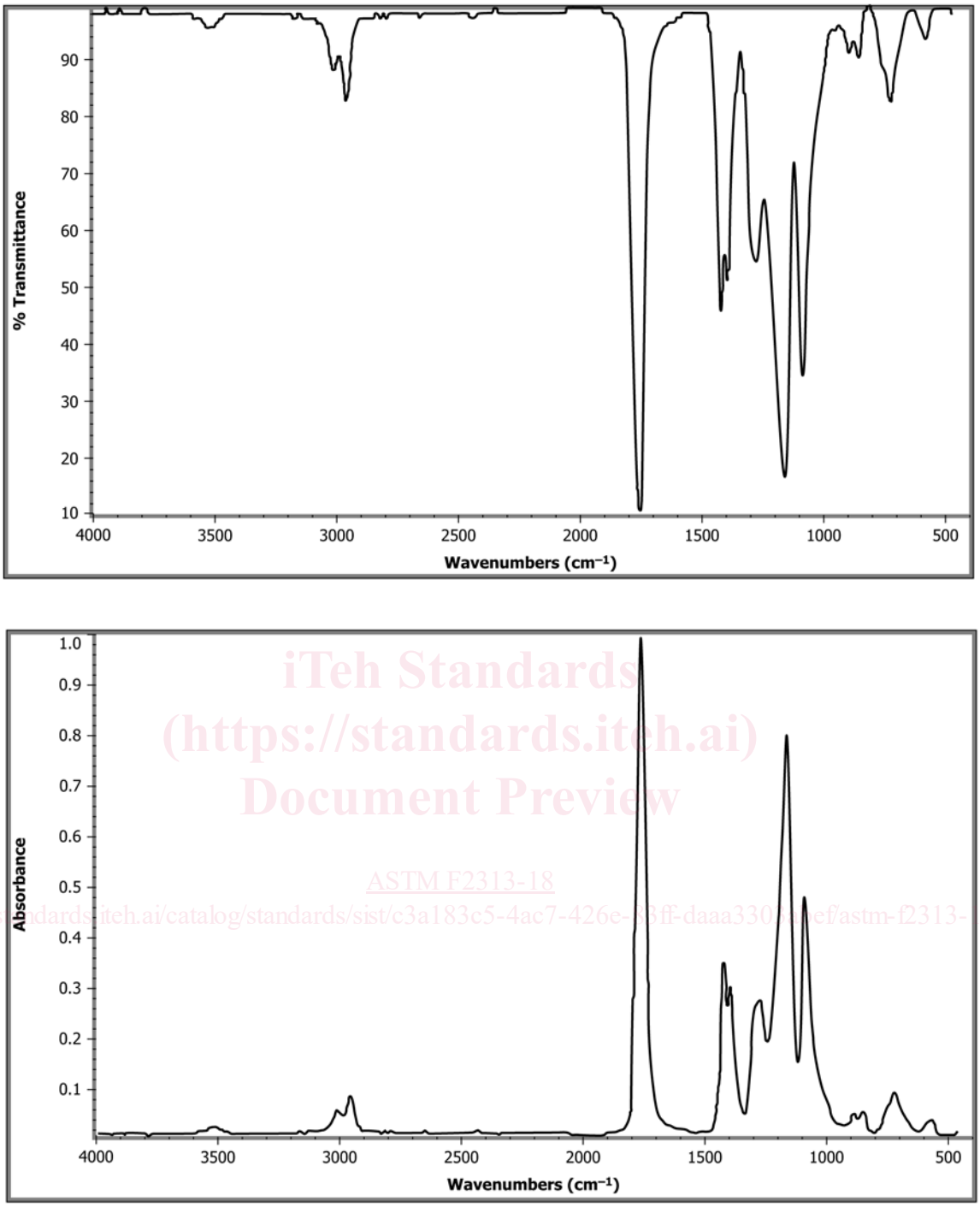
5.5 *Residual Solvents:*

5.5.1 If any solvent is utilized in any resin manufacturing or purification step, determine 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



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 (%)	Elemental Impurities (except catalyst)	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]	Report compliance per USP <232>[B]	Report per USP <233>[C]	±3 % of target (by mole)

[A] Utilizing a moisture determination method agreed upon by the supplier and the purchaser.
[B] See Section 5.6.3
[C] See Section 5.7.1 and Note 4.

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 instead 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 has 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 *Elemental Impurities:*

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

5.6.2 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.

5.6.3 Except for elements intentionally added as catalysts, assess the obtained results for compliance with the Parenteral Concentration limits described within the Individual Component Option of USP <232>, Table 3 (derived from ICH-Q3D Option 1, Table A.2.2). If all listed elements, except for those added as catalysts, can be 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 conform 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.

5.6.3.1 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.

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

5.7 *Residual Catalyst:*

5.7.1 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.

5.8 *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.