Designation: ~~F2579 – 10~~ 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~~ safety, health, and ~~health~~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*

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

Current edition approved ~~Dec. 1, 2010~~Dec. 15, 2018. Published ~~January 2011~~February 2019. Originally approved in 2006. Last previous edition approved in ~~2008~~2010 as ~~F2579 – 08.~~F2579 – 10. DOI: ~~10.1520/F2579-10.~~10.1520/F2579-18.

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

~~E386 Practice for Data Presentation Relating to High-Resolution Nuclear Magnetic Resonance (NMR) Spectroscopy (Withdrawn 2015)[3]~~

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

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

~~USP30/NF25~~USP 231 United States ~~Pharmacopeia (USP),~~Pharmacopeia: Chemical ~~May 2, 2007~~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(R3)~~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.

---

[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.

~~[5] 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~~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.

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 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 infra-red spectroscopy ~~practices~~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 ~~practices~~methods similar to those described in Practice ~~E386~~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 ~~practices~~methods similar to those described in Practice ~~E386~~E2977.

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

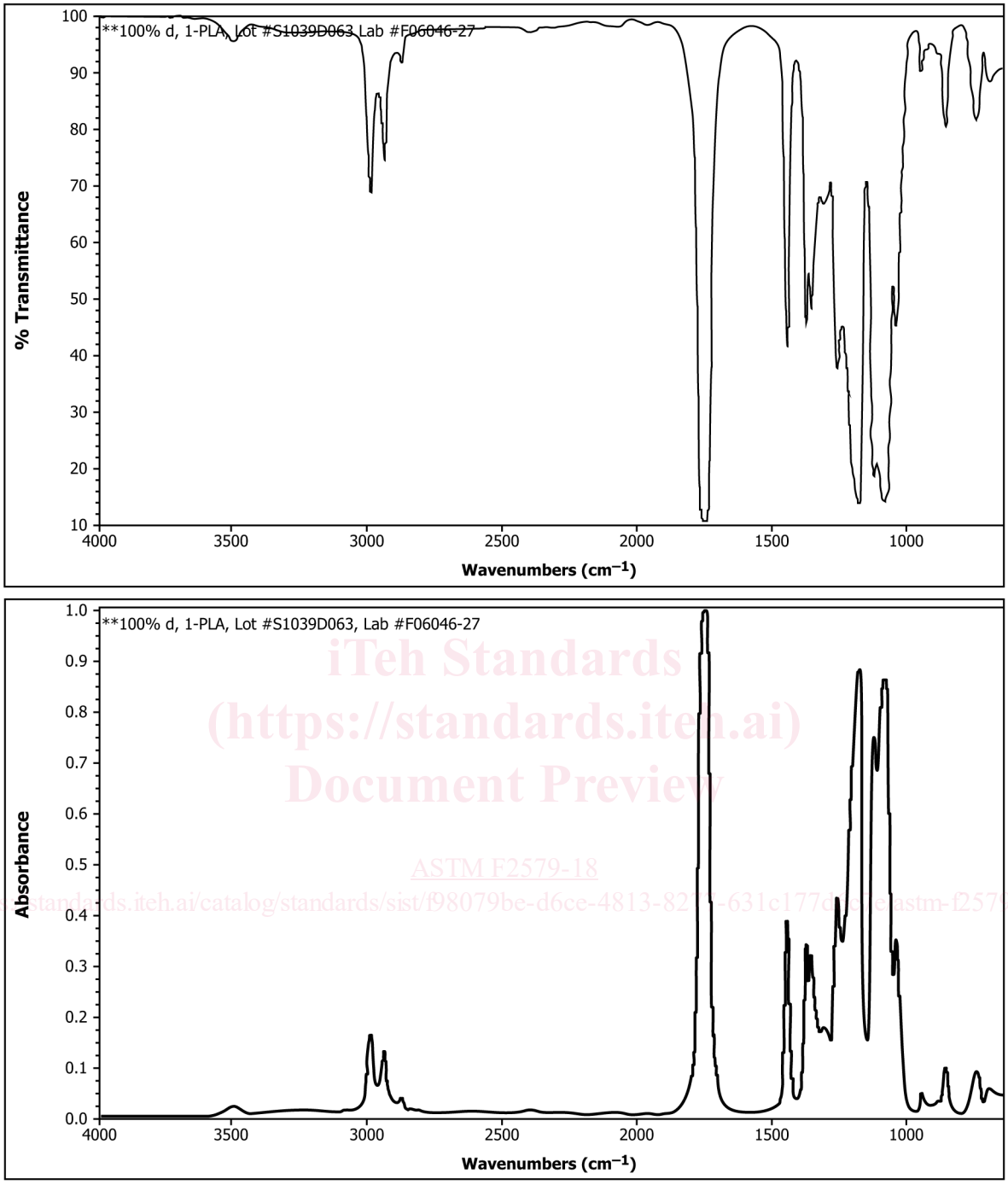
5.3 *Specific Rotation:*

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 ~~USP30/NF25~~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 ~~31-8~~],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 (IV).~~ 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.

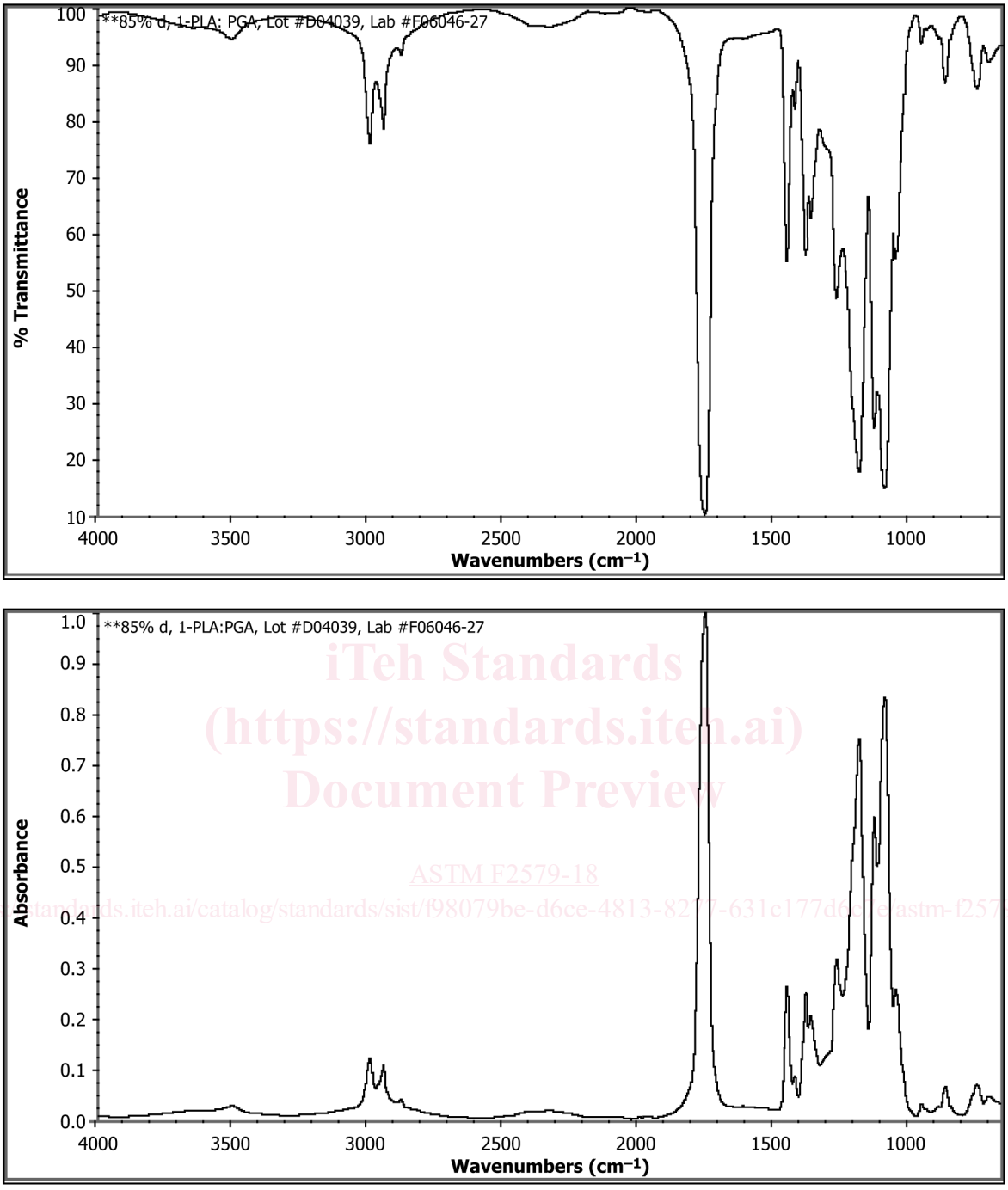


Example infrared spectra are alternative presentations of an amorphous 100 % DL-PLA homopolymer. (Spectra are courtesy of W. L. Gore & Associates, Inc., Flagstaff, AZ 86001, USA.)

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

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 dichloro-
methane (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.



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

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:

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

or

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