ASTM-FDA Workshop on Absorbable Medical Devices:

Standards Development in Absorbable Medical Devices

Presented by
- Byron Hayes – W.L. Gore

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FDA White Oak Campus
Silver Spring, Maryland, US
Disclosures

- Full time employee of W.L. Gore & Associates
  - Working with absorbables since 1980s
- ASTM-International
  - Chair - ASTM F04.97 Editorial & Terminology Subcommittee
  - Co-Chair - ASTM F04.11.05 Absorbable Polymers Task Group
  - Secretary – ASTM F04.42 – Biomaterials & Biomolecules for TEMPs
  - Participating Member: F04.30 Absorbables Task Group
- ISO (International Standards Organization)
  - Member: ISO-TC150/SC2/WG7 (Cardiovascular Absorbable Implants)
  - TC150/SC2 Liaison To TC194 (pending TC194 Confirmation)
  - Note: ISO Membership via AAMI
Overview of Presentation

• Introduction/Presentation Objective
  – Scope: Provide overview of major existing and upcoming American (USP & ASTM) and ISO absorbable Standards

• Early Absorbable History/Standardization

• Current Absorbable Standards (by Content)
  – General Characterization Standards
  – Degradation Characterization Standards
  – Raw Material Standards
  – Device/Application Specific Standards

• Absorbable Standards (Under Development)
  – Both in ASTM and in ISO TC150

• Other Absorbable Related Activities
  – ISO TC194 (10993 related)
Early Absorbable History/Standardization

- Broadly includes:
  - Natural polymers (e.g. collagen)
  - Synthetic polymers & copolymers
    - Typically w/a-hydroxy-esters (PGA, PGA/PLA)
  - Corrodible Metals/Alloys
    - Typically Mg° or Fe° based
- Perception: a new technology???
Early Absorbable History/Standardization (cont’d)
- Sutures

- Sutures
  - Likely oldest & most common device after the knife
  - Wound closure dates back to 5000-3000 BC to the origins of surgery

- Absorbable Sutures
  - First Use in Roman Empire
    - Sheep gut guitar strings (~120 AD – Galen)
  - First Scientific Observation
    - Leather band aids absorbed (Philip Syng Physick, 1768-1837)
      - First professor of surgery at the University of Pennsylvania
      - First in vivo Confirmation (1867 - Lister – in horse )
- Sutures

- Iron sutures (mid 1800s)
  - Art. 140. — *On the use of Iron-thread Sutures and Splints in Yesico-vaginal Fistula.*
  - Simpson. *(Medical Times and Gazette, Dec. 4, 1858.)*

- Collagen (catgut) Sutures
  - Sterile via carbolic acid (Lister 1868)
  - Heat sterile (Davis & Geck – 1913)
    - in tubes after sutures inside
    - Source: Archives & Special Collections at the Thomas J. Dodd Research Center
  - Chromic cat gut (germicide)
    - state of art for WWII
Early Absorbable History/Standardization (cont’d)

- Sutures/Polymer

  - First synthetic (a-hydroxy ester) absorbable sutures: DEXON® (D&G) & VICRYL® (Ethicon)
    - introduced in early 1970s
      - PGA (stiff polymer) => braided construction

Synthetic Absorbable Properties

- Broad Range of Longevity
  - PGA; PGA:PLA (3-4 months)
  - D,L-PLA Copolymers (1-16 months)
  - L-PLA Polymers (years)

- Same basic polymer technology in today’s newest orthopedic & cardiovascular devices
Early Absorbable History/Standardization (cont’d)
- US Regulatory Activity

- Collagens, DEXON®, VICRYL® commercially introduced prior to establishment of CDRH
  - Medical Device Amendments of 1976 (to the 1938 Food Drug & Cosmetics Act) - signed by President Gerald Ford
    - Established FDA Center for Devices and Radiologic Health
  - Many devices unregulated prior to 1976

- Sutures needed regulation => drug
  - Result, all (absorbable & nonabsorbable) sutures were approved via NDA (New Drug Application)

DEXON is a registered trademark of United States Surgical (a part of Covidien AG, Switzerland)
VICRYL is a trademark of Ethicon (a subsidiary of Johnson & Johnson)
**Early Absorbable History/Standardization (cont’d)**

- US Pharmacopeia (USP) Suture Standards

  - 1938 Federal Food & Cosmetic Act
  - USP to provide official standards of strength, quality, purity, packaging, and labeling enforced by FDA.
  - USP includes suture (device) monographs:
    - "Absorbable Surgical Suture"
    - "Nonabsorbable Surgical Suture"

**Trademarks**

- SOFSILK and TI-CRON are trademarks of United States Surgical (a part of Covidien AG, Switzerland)
Early Absorbable History/Standardization (cont’d)
- USP Absorbable Suture Monograph

- Covered basic requirements
  - Packaging and storage
  - Labeling
  - Length
  - Diameter
  - Knot-Pull Tensile Strength
  - Sterility <71>
  - Needle attachment
  - Soluble chromium compounds
Similar provisions established in European Pharmacopeia

- English version uses “absorbable”
- French version uses “résorbables”

Source: European Pharmacopoeia (74)
Early Absorbable History/Standardization (cont’d)
- US-FDA

• 1977 - Sutures reclassified from drug to Class III device (PMA instead of NDA)
  – “Transitional Device” in accordance with provisions of 1976 Act

• Late 1980s to 1990s - Sutures reclassified again from Class III device to Class II device
  • 1986 - Stainless steel suture
  • 1988 - Absorbable surgical gut suture
  • 1989 - Absorbable poly(glycolide/L-lactide) surgical suture
  • 1990
    • Nonabsorbable poly(ethylene terephthalate) surgical suture
    – Nonabsorbable polypropylene surgical suture
    • Nonabsorbable polyamide surgical suture
    • Natural nonabsorbable silk surgical suture
  • 1999 - Nonabsorbable expanded polytetrafluoroethylene surgical suture

Early Absorbable History/Standardization (cont’d)
- US-FDA (1990s)

- US-FDA - Code of Federal Regulations currently describe:

<table>
<thead>
<tr>
<th>Suture Name</th>
<th>Regulation</th>
<th>Procde</th>
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<tbody>
<tr>
<td>Absorbable Polydioxanone Surgical (PDS) Suture</td>
<td>21 CFR §878.4840</td>
<td>NEW</td>
</tr>
<tr>
<td>Absorbable Poly(glycolide/L-lactide) Surgical Suture</td>
<td>21 CFR §878.4493</td>
<td>GAM</td>
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<tr>
<td>Absorbable Gut Suture</td>
<td>21 CFR §878.4830</td>
<td>GAL</td>
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<tr>
<td>Nonabsorbable Poly(Ethylene Terephthalate) Suture</td>
<td>21 CFR §878.5000</td>
<td>GAT</td>
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<tr>
<td>Nonabsorbable Polypropylene Surgical Suture</td>
<td>21 CFR §878.5010</td>
<td>GAW</td>
</tr>
<tr>
<td>Nonabsorbable Polyamide Surgical Suture</td>
<td>21 CFR §878.5020</td>
<td>GAR</td>
</tr>
<tr>
<td>Natural Nonabsorbable Silk Surgical Suture</td>
<td>21 CFR §878.5030</td>
<td>GAP</td>
</tr>
<tr>
<td>Stainless Steel Surgical Suture</td>
<td>21 CFR §878.4495</td>
<td>GAQ</td>
</tr>
<tr>
<td>Nonabsorbable Expanded Polytetrafluoroethylene (ePTFE) Surgical Suture</td>
<td>21 CFR §878.5035</td>
<td>NBY</td>
</tr>
</tbody>
</table>

- Current Federal Regulations cover:
  - Composition
  - Meet USP requirements
  - Class II Device
Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Surgical Sutures

Document issued on: June 3, 2003

1. INTRODUCTION
2. BACKGROUND
3. THE CONTENT AND FORMAT OF AN ABBREVIATED 510(K) SUBMISSION
4. SCOPE
5. DEVICE DESCRIPTION
6. RISKS TO HEALTH
7. BIOCOMPATIBILITY
   • Directly: ISO10993 Parts 1, 5 (in vitro cytotox), & 10 (irritation/sensitization)
8. STERILITY
   • Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA
9. PHYSICAL/PERFORMANCE CHARACTERISTICS
   • Includes: USP requirements and degradation/resorption profile (absorbables)
10. CLINICAL STUDIES
    • Only if a new material, technology, or indication
Current Absorbable Standards
- General Characterization

• Polymers
    – general guidelines for the chemical, physical, mechanical, biocompatibility, and preclinical assessments of implantable synthetic polymeric absorbable devices or implant components.
    1) Includes:
       a) Fabrication & Processing Related Features & Considerations
       b) Device Characterizations/Assessments (Composition, Mechanical, etc.)
       c) Packaging, Sterility, Shelf-Life, & Labeling
       d) Biocompatibility Considerations
    2) Approved for publication - possible by end of 2012

• Metals
  • no equivalent standard for implants
Current Absorbable Standards - Degradation Characterization

- **Polymers (Hydrolysis)**
  - ISO 13781 - Poly(L-lactide) resins and fabricated forms for surgical implants — *in vitro* degradation testing
  - ISO 15814 - Implants for surgery — Copolymers and blends based on polylactide — *in vitro* degradation testing
    - Common features: Covers hydrolysis conditions (including buffer solutions)
    - Both ISO standards now under revision, may be combined into a single document

- **Metals (Corrosion)**
  - No equivalent (absorbable implant specific) standard
  - No developed consensus on what corrosion model is best representative of *in vivo* &/or clinical conditions
    - part of a broader deficiency of corrosion modeling
    - Consensus => *in vivo* studies provide the best estimate
Current Absorbable Standards - *in vivo* Evaluations

- **ASTM F1983 - Standard Practice for Assessment of Compatibility of Absorbable/Resorbable Biomaterials for Implant Applications**
  - Describes *in vivo* biological assays of tissue reactions to absorbable/resorbable implantable biomaterials.

- **ISO 10993-6 - Tests for local effects after implantation**
  - Covers *in vivo* assessment of the biological safety of a material
  - Contains numerous absorbable provisions
Current Absorbable Standards - Raw Materials

- **Natural Derived Polymers**
  - ASTM F2212 - Standard Guide for Characterization of Type I Collagen as Starting Material for Surgical Implants and Substrates for Tissue Engineered Medical Products (TEMPs)
- **Synthetic Polymers**
  - ASTM F2313 - Standard Specification for Poly(glycolide) and Poly(glycolide-co-lactide) Resins for Surgical Implants with Mole Fractions Greater Than or Equal to 70 % Glycolide
  - ASTM F2579 - Standard Specification for Amorphous Poly(lactide) and Poly(lactide-co-glycolide) Resins for Surgical Implants
- **Primary & unifying features:**
  - Molecular weight evaluation through Inherent viscosity testing
    - PGA-rich polymers are marginally soluble; require aggressive & expensive toxic solvents (solvent drives separation from PLA)
  - Thermal characterization (crystallinity, Tg)
- **ISO** – has no known absorbable raw material standards
Current Absorbable Standards
- Raw Materials

• Metals
  – Numerous - not aware of specific to absorbable implantables
  – e.g. Magnesium/Mg-alloys
    • (i) ISO 3116 Magnesium and magnesium alloys - Wrought magnesium alloys
    • (ii) ASTM B 80-01 “Standard Specification for Magnesium-Alloy Sand Castings”
    • (iii) ASTM B 107/B 107M Standard Specification for Magnesium-Alloy Extruded Bars, Rods, Profiles, Tubes, and Wire
  – General metallic standards (independent, if corrodible or not)
    • (i) EN 10002-1 Metallic materials - Tensile Testing Part 1: Method of testing at ambient temperature
    • (ii) EN 10204 Metallic products - Types of inspection documents
    • ASTM E 112 Standard test methods for determining average grain size
    • (iv) ASTM B 557a Standard Test Methods of Tension Testing Wrought and Cast Aluminium- and Magnesium-Alloy Products
    • (v) ASTM B954 Standard test methods for chemical analysis of magnesium and magnesium alloys by atomic emission spectrometry
    • (vi) ASTM B953 Standard practices for sampling magnesium and magnesium alloys for spectro-chemical analysis
Current Absorbable Standards - Device/Application Specific

- **Sutures**
  - USP, European Pharmacopeia, US-FDA as previously described

- **Orthopedic**
  - **ASTM F2502 - 11 Standard Specification and Test Methods for Absorbable Plates and Screws for Internal Fixation Implants**
    - Covers torsional, pullout, and bend testing

- **TEMPs (Tissue Engineered Medical Products)**
    - Covers characterization of micro-porous (typically) absorbable scaffolds
Current Absorbable Standards
- Device/Application Specific (Cardiovascular)

- ASTM F04.30 – Subcommittee on Cardiovascular
- ASTM WK35909 (*under development*) - Standard Guide to Testing of Absorbable Stents and Stent Grafts
  - Adjusts for absorbable aspects of testing:
    - INTRINSIC ELASTIC RECOIL (F2079)
    - STENT SECUREMENT (F2394)
    - THREE-POINT BENDING (F2606)
    - FATIGUE TO FRACTURE (*pending* WK29690)
    - RADIAL LOADING (*pending* WK34602)
  - Unifying features
    - Sample conditioning, evaluation timing
Current Absorbable Standards - Device/Application Specific (Cardiovascular)

- ISO TC150/SC2/WG7 - Cardiovascular Absorbable Implants
  - TC150 = Implants for Surgery
  - SC2 = Cardiovascular Implants and Extracorporeal Systems
  - WG7 = Cardiovascular Absorbable Implants

- Developing a guide to absorbable related:
  - Design Evaluation Requirements
  - in vitro Acute Assessment
  - in vitro Chronic Assessment
  - in vitro/in vivo Correlation
    - Drug-Absorbable Component Interactions
  - Biocompatibility
  - Preclinical in vivo Evaluation
  - Clinical Evaluation
  - Shelf-life Considerations

Current Absorbable Standards – Terminology [per ASTM F2902]

- absorbable (adj.) --- *in the body*, an initially distinct foreign material or substance that either directly or through intended degradation can pass through or be metabolized or assimilated by cells &/or tissue.

  Can be absorbed, *not necessarily excreted*

- Use of “absorbable” and “nonabsorbable” sutures dates back at least to 1921 (numerous use instances in OFFICIAL JOURNAL OF AMERICAN COLLEGE OF SURGEONS, Volume XXXII APRIL, 1921 Number 4.)
Thank you for your time