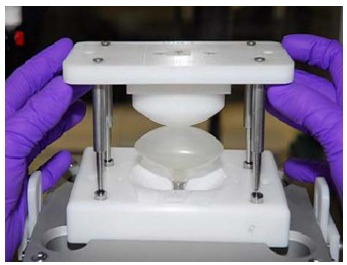

Challenges and Experiences in Using New Materials

Bob Ward	**President/CEO, DSM PTG**
Joseph Chinn	**Owner, J Chinn LLC**
Jennifer Neff	**CEO/CTO, Allvivo Vascular**
Janine Robinson	**VP Research, Articulinx, Inc.**
Ming Wu	**VP Eng., Edwards Lifesciences**

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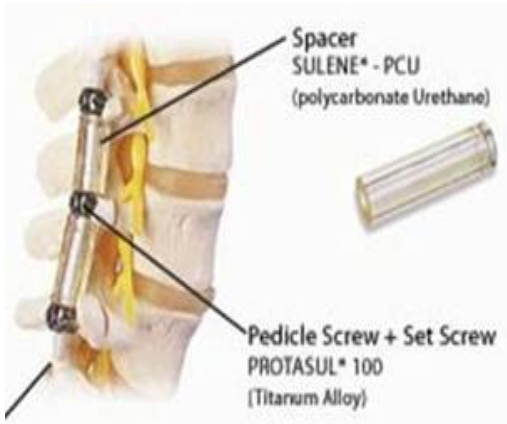
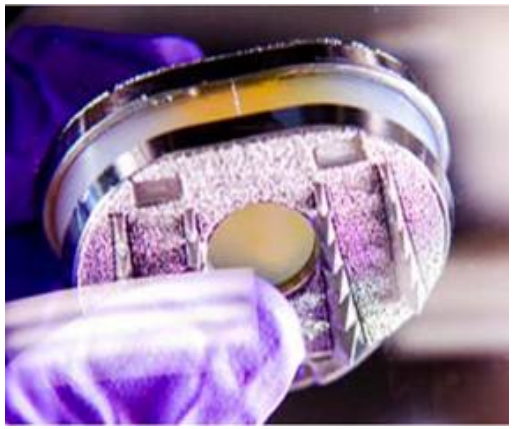
New Materials in Orthopedic Implants

Dynamic Spinal Fixation



Cervical Spinal Disc



Lumbar Spinal Disc

Hip Joint

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Integration of Material and Device Development

Lab and Pilot-Scale Synthesis

Production-Scale Synthesis

Characterization and QC

Component Fab.

Device Assembly

1. Why use a new material?

- Satisfy bulk and surface property requirements of a device
- Obtain a performance advantage (over competitive devices)
- Replace an unreliable or unwilling supplier
  - Improve lot-to-lot consistency
  - Support a chronic implant application
- Improve device manufacturing process
  - Reduce COGs
- Strengthen IP position
- Facilitate regulatory approval
  - Establish(ed) Master File
  - ISO and cGMP Quality Systems

How does FDA view new materials?

2:40 – 3:20 P.M. Room 210 B

Risk Management and Assessment in Sourcing and Working with New Materials

Jennifer A. Neff, CEO, CTO Allvivo Vascular, Inc.

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Evaluation and Testing Within a Risk Management Process: ISO 10993-1:2009 (E)

Table A.1 — Evaluation tests for consideration

Medical device categorization by			Biological effect							
nature of body contact (see 5.2)		contact duration (see 5.3) A – limited (≤ 24 h) B – prolonged (> 24 h to 30 d) C – permanent (> 30 d)	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Systemic toxicity (acute)	Subchronic toxicity (subacute toxicity)	Genotoxicity	Implantation	Haemocompatibility
Category	Contact									
Surface device	Skin	A	X [a]	X	X					
		B	X	X	X					
		C	X	X	X					
	Mucosal membrane	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
	Breached or compromised surface	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
External communicating device	Blood path, indirect	A	X	X	X	X				X
		B	X	X	X	X				X
		C	X	X		X	X	X		X
	Tissue/bone/dentin	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Circulating blood	A	X	X	X	X				X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X
Implant device	Tissue/bone	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Blood	A	X	X	X	X	X		X	X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X

[a] The crosses indicate data endpoints that can be necessary for a biological safety evaluation, based on a risk analysis. Where existing data are adequate, additional testing is not required.

2. What can the material supplier do to help?

- **Data and Design Support**
  - **Liability**
- **Samples**
- **Processing Assistance**
- **Support of Regulatory Process**
  - **Quality Sytems**
  - **Material Master File**

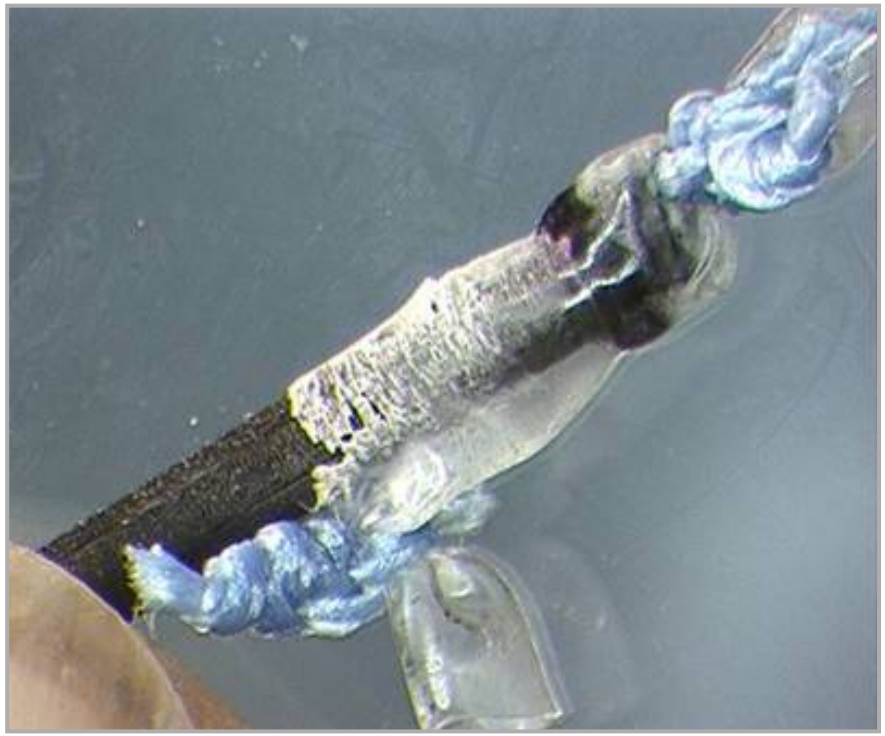
3. How can you help your material supplier?

- **Would you consider supplying your (device) biocompatibility test results to the material supplier for inclusion in *confidential* FDA Material Master Files?**

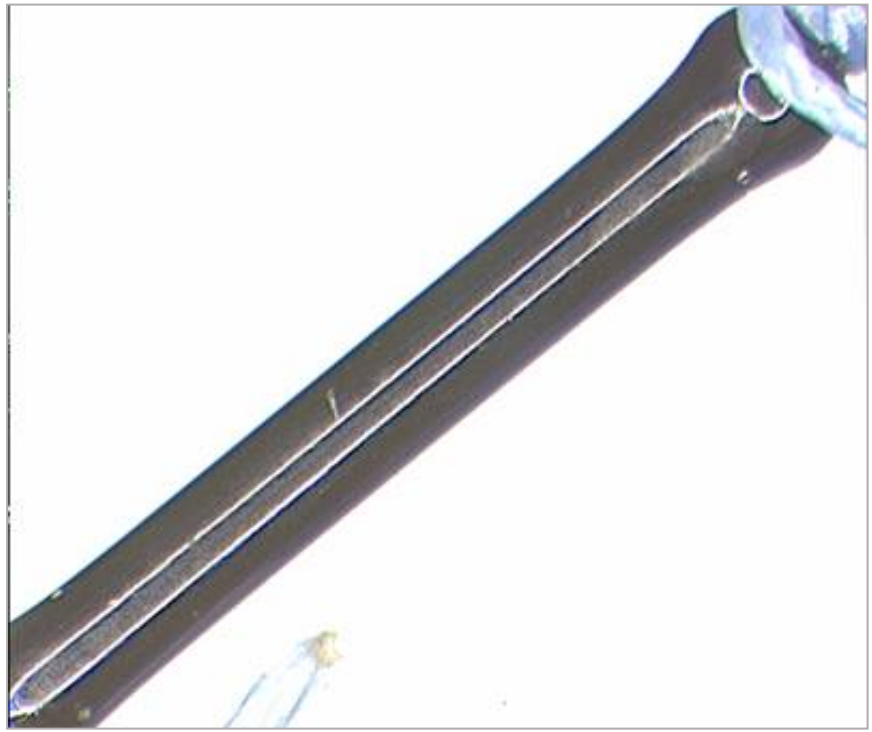
4. Evolution or Revolution?

- **Is continual improvement and/or modification of established biomaterials preferable to the use of entirely new materials?**
  - **Surface Modification**
    - **Improved biostability**
  - **Property Enhancement**
  - **Processing Improvements**
    - **Gel Reduction**
    - **Better Injection Molding**
  - **Lot-to-lot Consistency**
  - **Expanding Master File**

Improved Biostability: Fluorocarbon End Groups Reduce Environmental Stress Cracking of otherwise identical 80A Polyether-urethanes in Intramuscular Rabbit Implants @ 400 % Strain



Polyether-urethane Control: 3-month explant



Polyether-urethane with fluorocarbon end groups: 6-month explant

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Thank You

DSM Biomedical

Hall D

Booth #2449

www.dsmptg.com

DSM PTG

2810 7th Street

Berkeley, CA 94710

(510)841-8800

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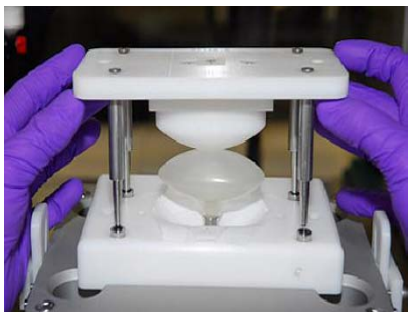
Evolution vs Revolution



Evolution of Thermoplastic Biomedical Polyurethanes:

Continual Improvement of Existing Material Platforms

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Continuous Improvement of Thermoplastic Polyurethanes for Chronic Implants

Platform Compositions

- Aromatic (MDI) Polyether-urethane
  - Strong and hydrolytically stable
- Aromatic (MDI) Polycarbonate-urethanes
  - Very strong and oxidatively stable (when ether free)

DSM PTG Enhancements

Via Composition Changes

- Mixed Soft Segments: Silicone-urethane copolymers with enhanced biostability (ca. 1989)
- Use of surface activity and self assembly (of end groups) for surface modification:
- Ether-free soft segments
  - Improved oxidative stability
  - Increased toughness

Continuous Improvement of Thermoplastic Polyurethanes for Chronic Implants

DSM PTG Enhancements

Via Processing Improvements:

- **Replace batch synthesis with continuous synthesis by reactive extrusion**
  - **On-line feedback for MW control**
  - **Reduced particulates**
  - **Rapid development of custom polymers**

- **Gel reduction technologies for higher yields**
  - **During polymer synthesis**
  - **During extrusion of tubing**

Some DSM PTG Thermoplastic Polyurethanes

Bionate® polycarbonate-urethane

- **CarboSil®** silicone-polycarbonate-urethane
- **CarboSil® AL** aliphatic silicone-polycarbonate-urethane
- **Bionate®II** polycarbonate-urethane (PCU) with SAME® technology

Elasthane™ polyether-urethane with low MW wax

- **PurSil®** silicone-polyether-urethane
- **PurSil® AL** aliphatic silicone-polyether-urethane
- **Elasthane™II** polyether-urethane with SAME™ technology*

Note: All polymer families have FDA Master Files

*** Developmental material**

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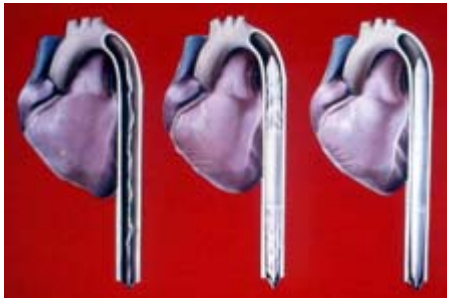
38 Years of Applications:
Polyurethanes in Blood Pumps



AVCO IAB 1971: First Clinical Cardiac Assist Device

Jarvik III TAH

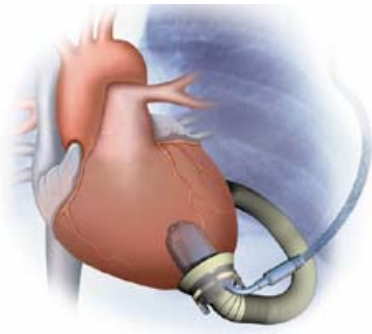
Abiocor TAH

Abiomed BVS

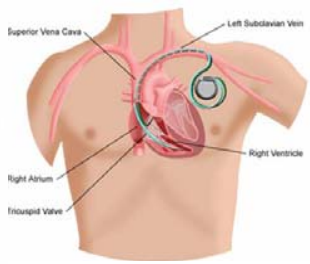
Thoratec PVAD and IVAD

TCS HeartMate® LVAD

Thoratec HeartMate II



Jarvik 2000



Pacemakers (Various)

Sunshine Heart C-Pulse™ 2009

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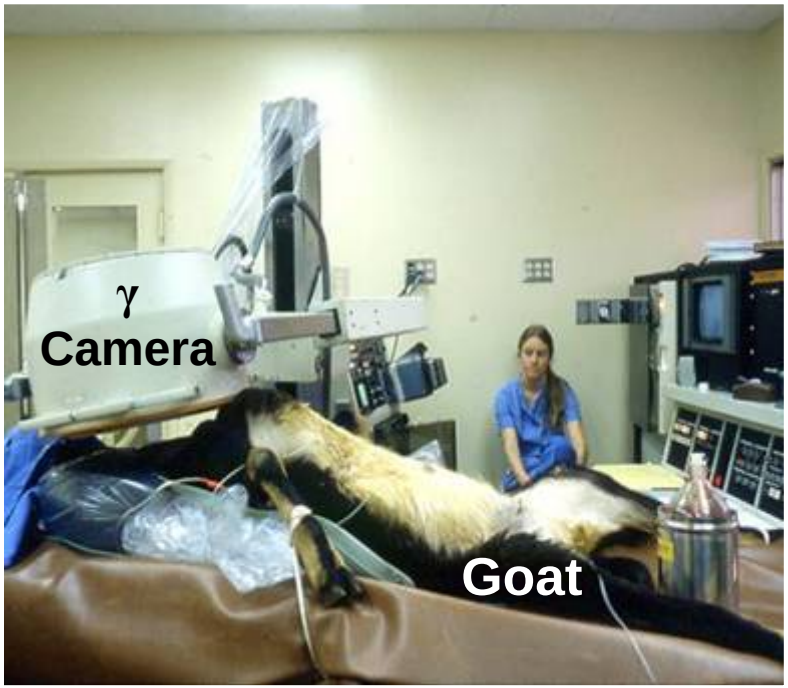
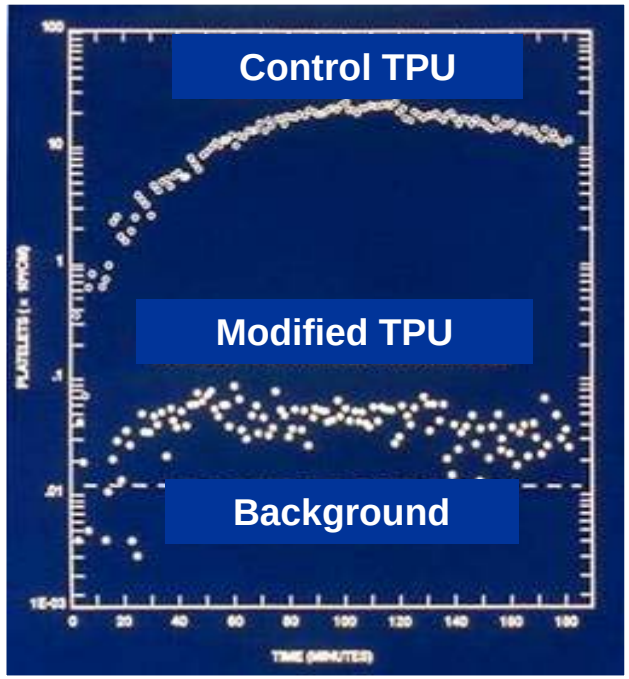
1.a. Improved Passive Thrombo-Resistance: *In Vivo* Platelet Thrombus on Catheters is Reduced Three Orders of Magnitude by a Polymeric Surface Modifying Additive (SMA)

Experiment in Progress



Radiolabled Platelet Uptake vs time



1000-fold reduction in Adherent Platelets on Modified TPU Catheter

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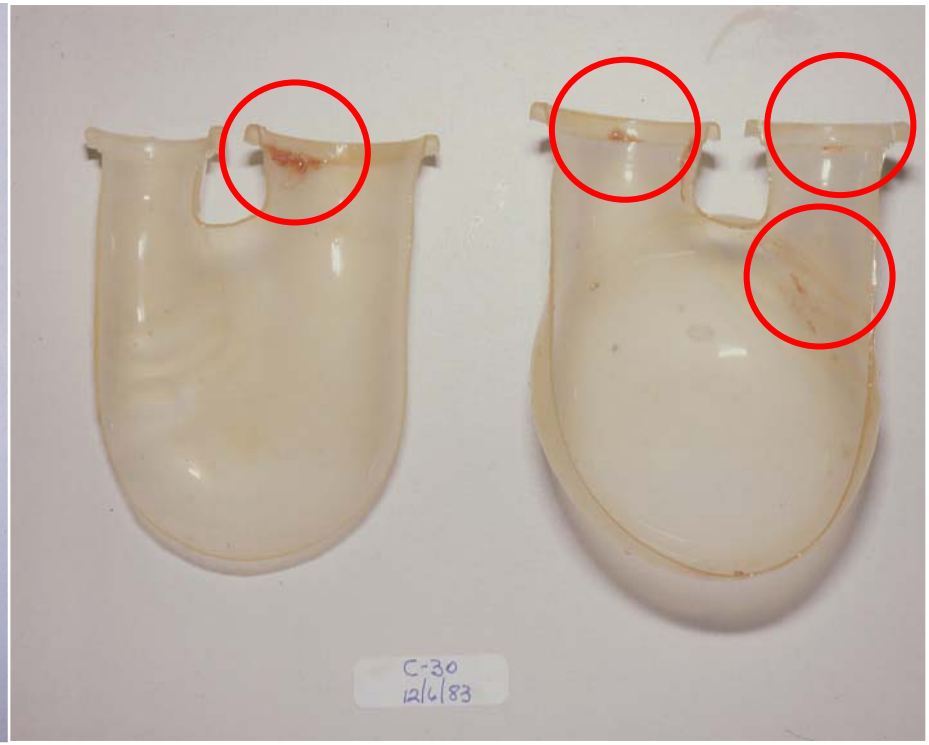
1.b. Improved Passive Thrombo-Resistance: Aherent Thrombi on In Vivo Sac-Type LVAD is Reduced with Surface Modifying Additive in Segmented Polyurethane-urea

VAD Blood Sacs: 30-day Calf Explants

SPU <u>with</u> Surface Modification



SPU <u>without</u> Surface Modification

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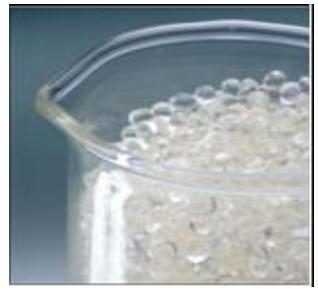
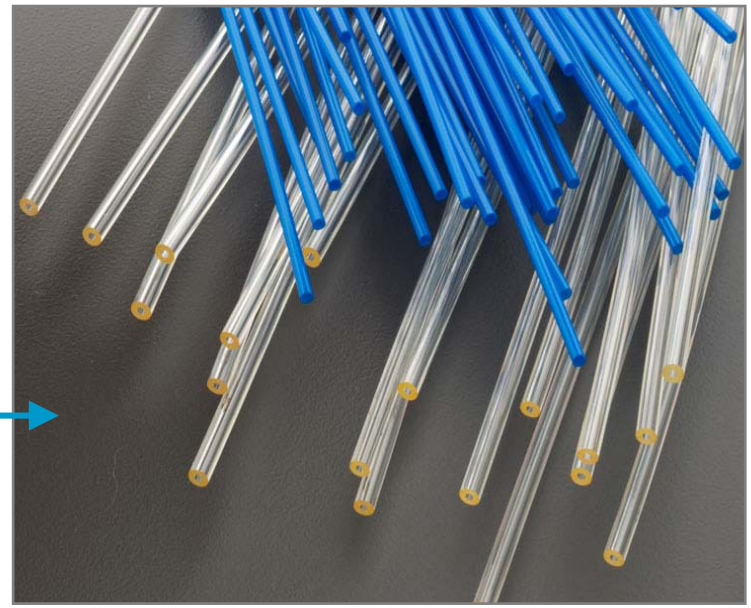
Three-Steps to Antimicrobial Tubing: *Tubing Extruded from Pre-dried 'SAME Polymer' Pellets Made by Continuous Synthesis*

1. Continuous Synthesis of Pellets

2. Dry Polymer Pellets



Tubing Ready for Use



3. Tubing Extrusion and Collection

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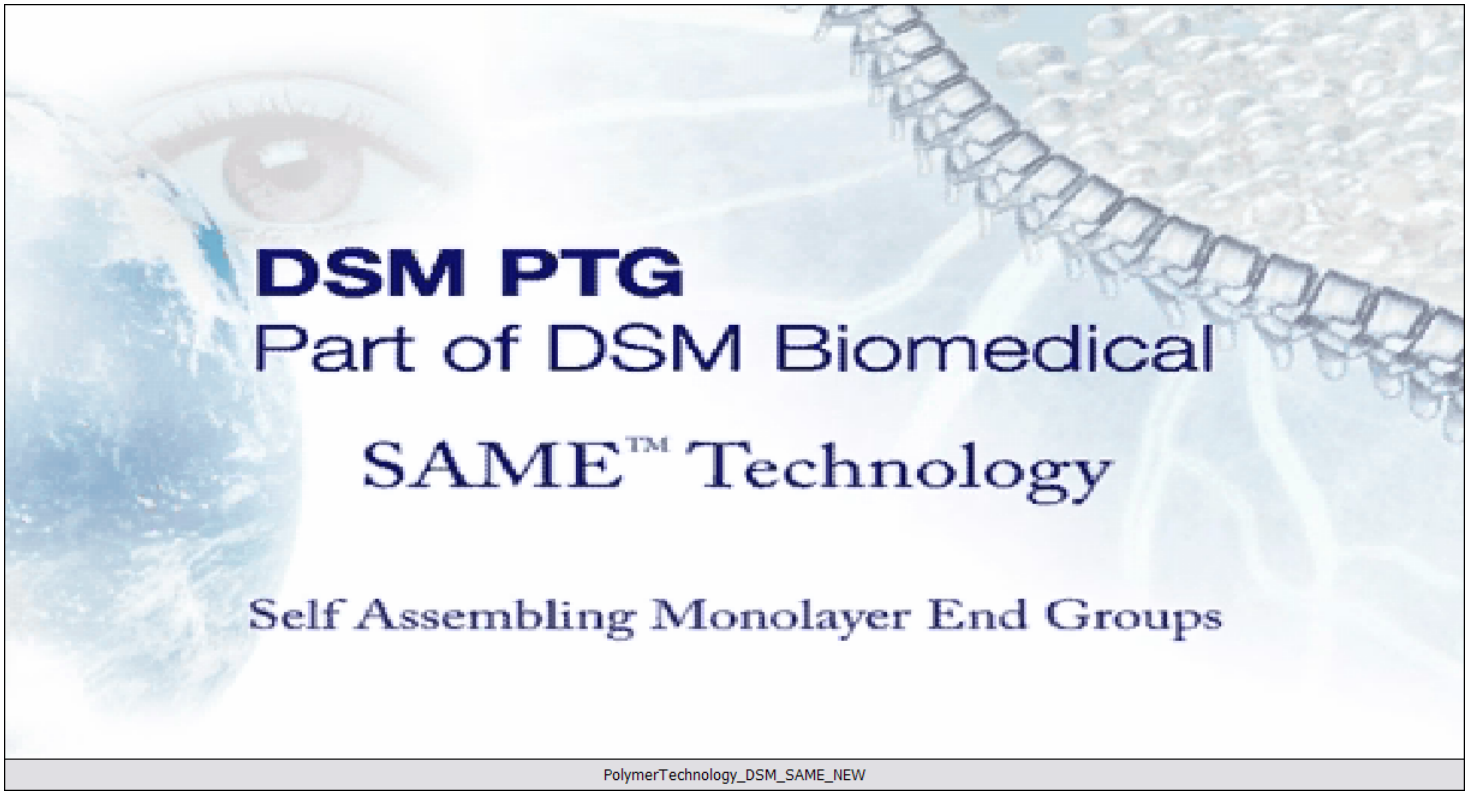
Self Assembling End Groups:

Self Assembly on Extruded Polyurethane Tubing, e.g. 'Bionate® II'



Not to scale

New Device Possibilities with End-Group-Modified Thermoplastics

- **Biomaterials must satisfy bulk *and* surface property requirements**
- **PUs with *Self Assembling Monolayer End Groups* (SAME™) are a 'Biomaterials Toolkit' for independently optimizing bulk *and* surface properties**
- **SAME™ technology has the potential to provide a simple and economical method for manufacturing tailored (e.g., antimicrobial) polymer surfaces without negative impact on polymer bulk properties.**
- **Antimicrobial and other SAME polymers can be easily integrated into medical device manufacturing when used as:**
  - **Neat Structural Materials**
  - **Surface-modifying additives to other base polymers**
  - **Coatings on other materials**

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