

# Improving Long-acting Dosage Forms with Biomaterials Innovation

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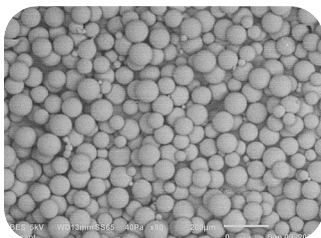
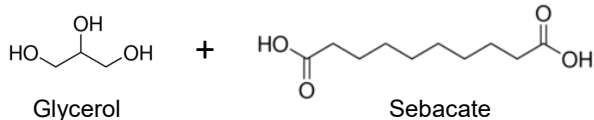
secant group

PARTNERS FROM INSPIRATION TO REALIZATION



# PGSU Biomaterial Advances

Poly(Glycerol Sebacate)



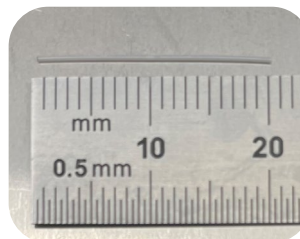
API-loaded PGSU microspheres



API-loaded PGSU subcutaneous implants



Peptide- & Protein-loaded PGSU implants



API-loaded PGSU ocular micro-implants



API-loaded PGSU gastroretentive oral dosage forms

Proprietary, scalable PGS resin synthesis



# Fabricating Hydrable (PGSU) Dosage Forms



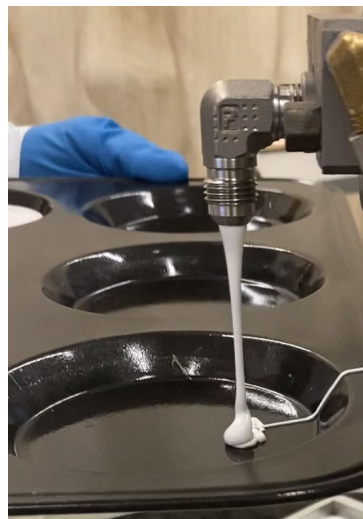
+



API powder dispersed into liquid PGS resin

Crosslinker  
Catalyst

<40 °C



Blend flowed into mold

Curing  
Demolding

23 °C  
10 min



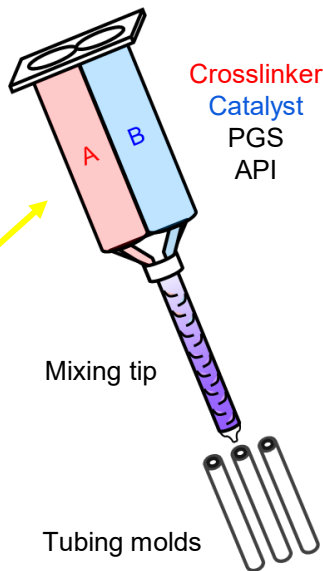
Drug-loaded elastomer removed from mold

# Manufacturing across Scales

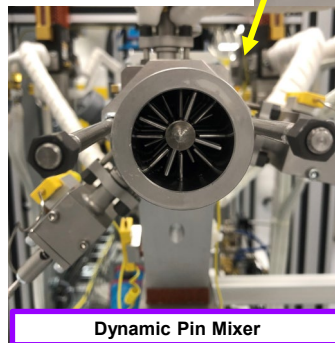
## Two-part Meter/Mix/Dispense Molding Process



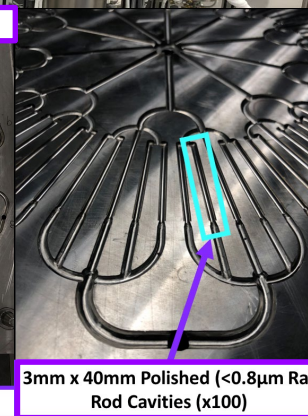
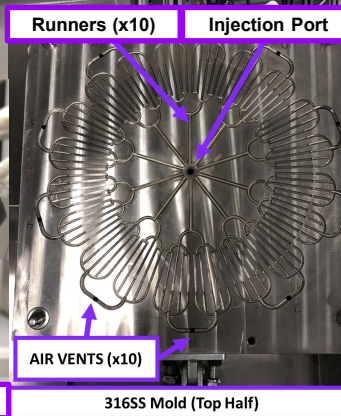
Dual-barrel syringe



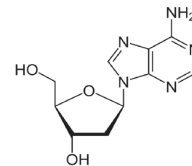
Bench → Pilot



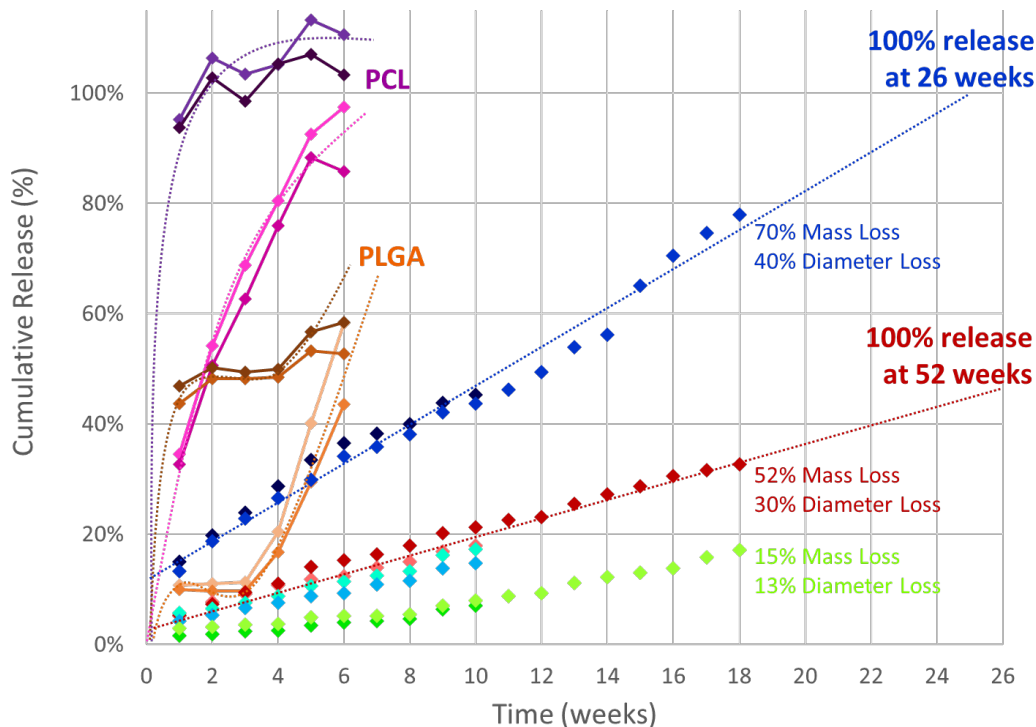
Dynamic Pin Mixer



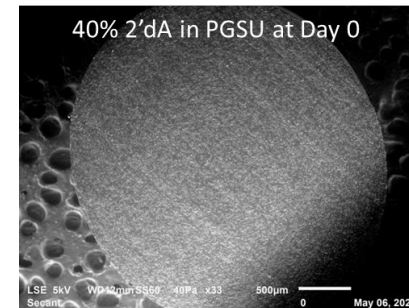
# Long-acting Subcutaneous Implants



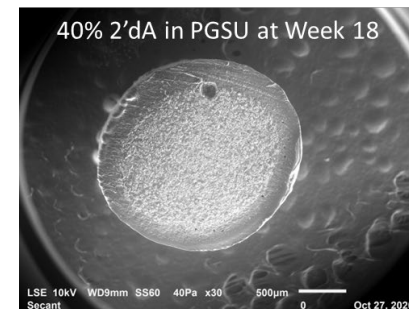
2'dA  
Solubility in  
dissolution  
media =  
25 mg/mL



- ◆ 40% 2'dA PCL
- ◆ 40% 2'dA PCL
- ◆ 60% 2'dA PCL
- ◆ 60% 2'dA PCL
- ◆ 40% 2'dA PLGA
- ◆ 40% 2'dA PLGA
- ◆ 60% 2'dA PLGA
- ◆ 60% 2'dA PLGA
- ◆ 60% 2'dA PGSU
- ◆ 60% 2'dA PGSU
- ◆ 40% 2'dA PGSU
- ◆ 40% 2'dA PGSU
- ◆ 20% 2'dA PGSU
- ◆ 20% 2'dA PGSU
- ◆ 10% 2'dA PGSU
- ◆ 10% 2'dA PGSU



Surface Erosion

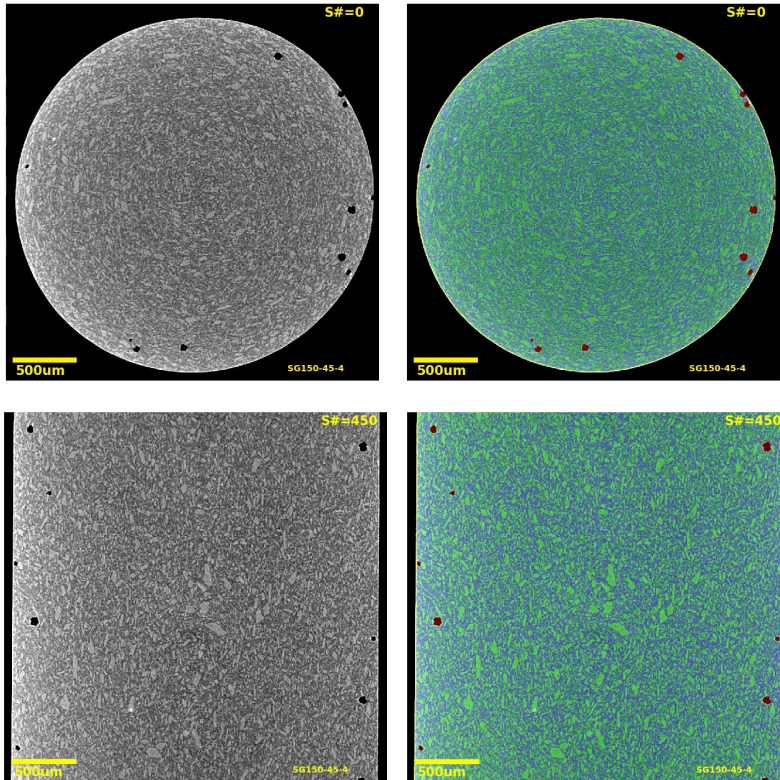


# Microstructural Imaging

50% 2'da PGSU implant

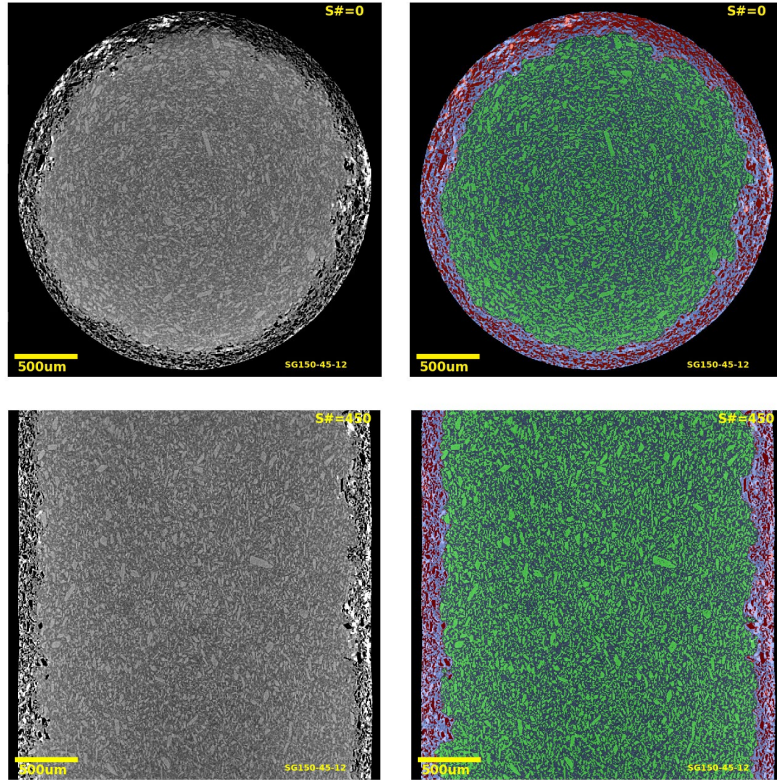


Pre-existing Pore | API | Polymer



Before Dissolution, t=0

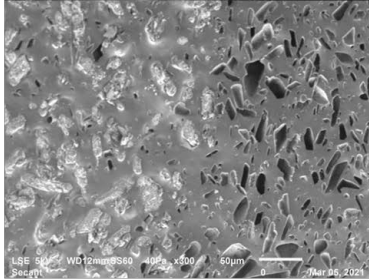
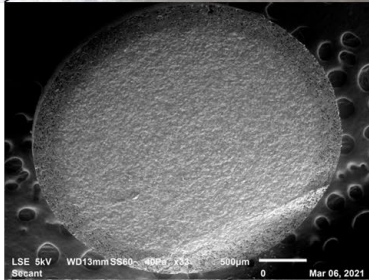
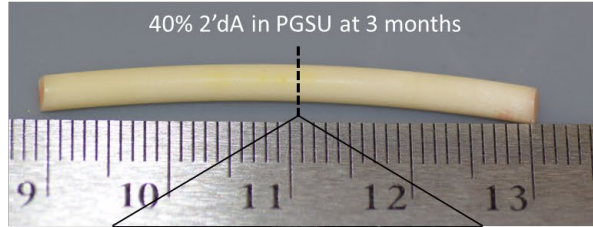
Outer Post-release Pore | Pre-existing Pore | API | Polymer



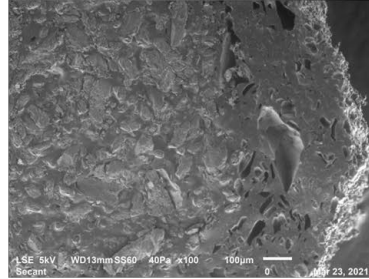
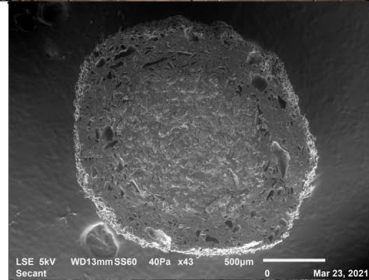
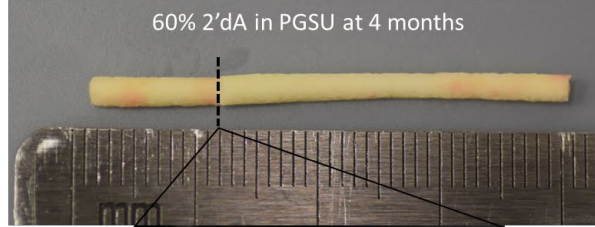
During Dissolution, 20% release, t=5 weeks

# Implant Retrievability

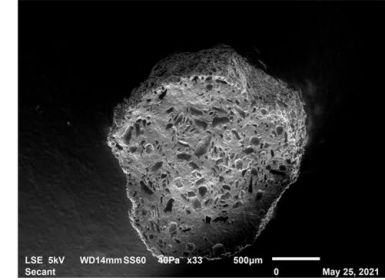
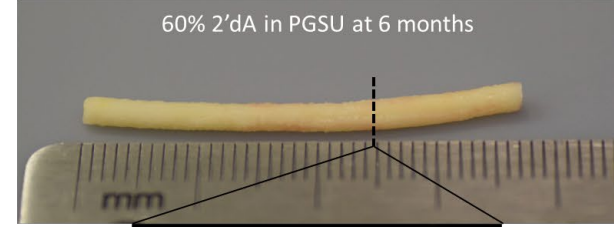
40% 2'dA in PGSU at 3 months



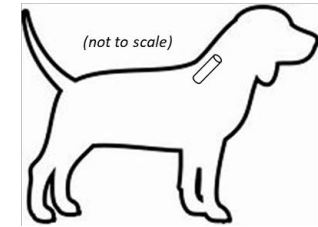
60% 2'dA in PGSU at 4 months



60% 2'dA in PGSU at 6 months



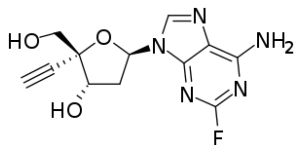
Beagle dog model, dorsal subcutaneous implantation



# Multi -purpose Prevention Technology (MPT) Implants

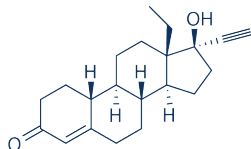
BILL & MELINDA  
GATES foundation

Calibr  
at Scripps Research



EFdA

Solubility in dissolution  
media = 900 µg/mL



Levonorgestrel

Solubility in dissolution  
media = 6 µg/mL

40% EFdA PGSU



2.4 x 15 mm

40/15% EFdA/LNG PGSU

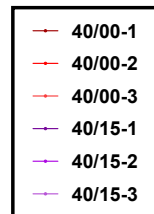
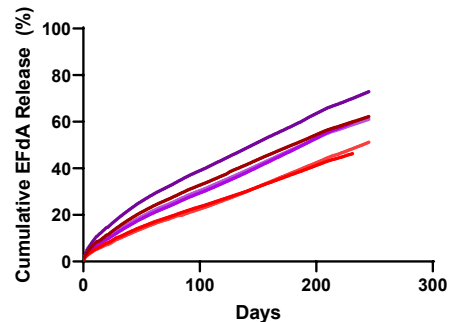
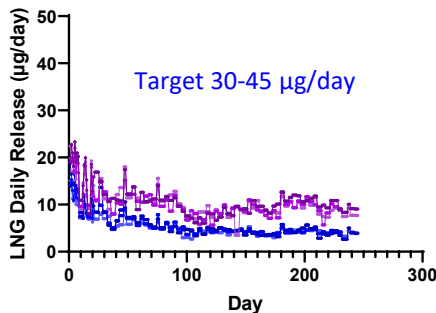
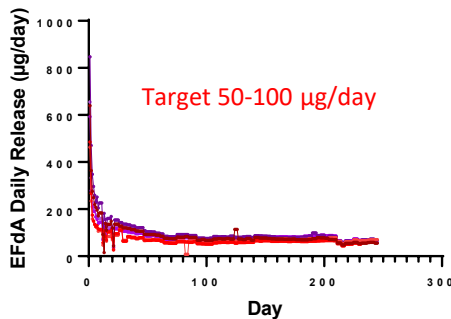


2.4 x 15 mm

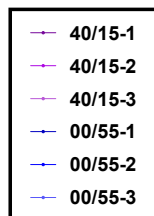
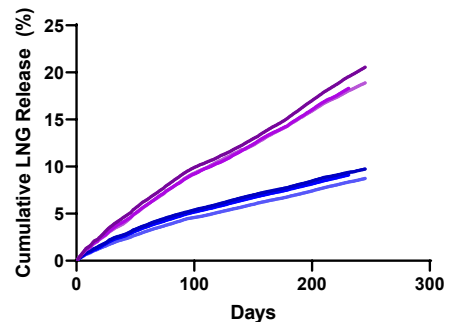
55% LNG PGSU



1.1 x 20 mm



PBS, pH 7.4, 37°C

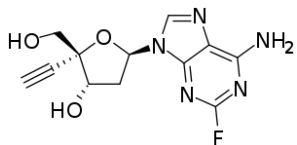




# Multi -purpose Prevention Technology (MPT) Implants

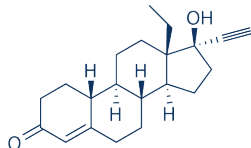
BILL & MELINDA  
GATES foundation

Calibr  
at Scripps Research



EFdA

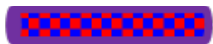
Solubility in dissolution  
media = 900 µg/mL



Levonorgestrel

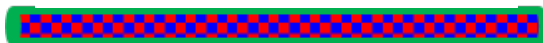
Solubility in dissolution  
media = 6 µg/mL

40/15% EFdA/LNG PGSU

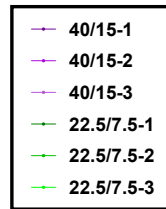
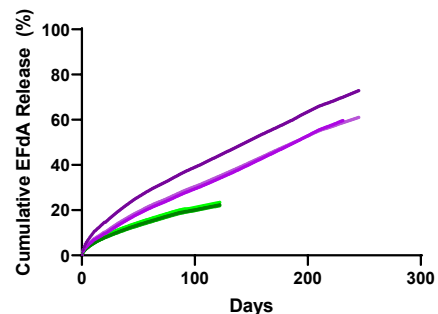
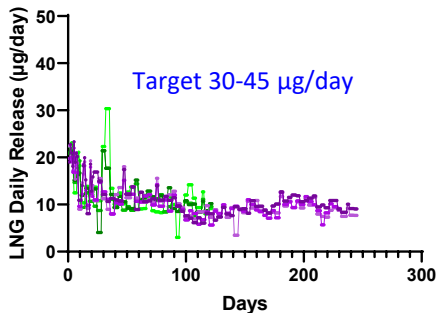
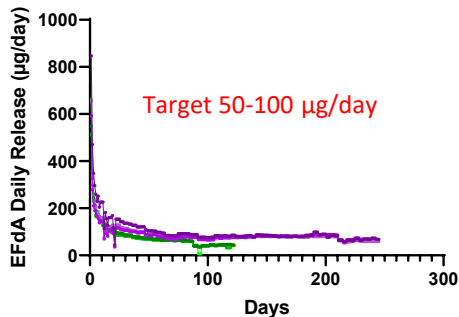


2.4 x 15 mm

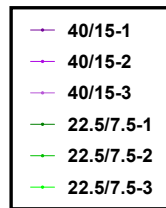
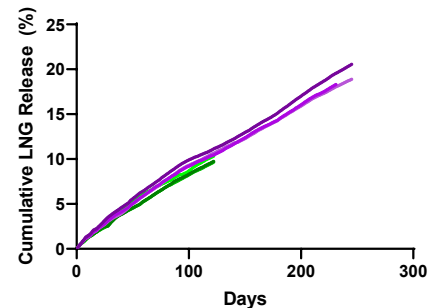
22.5/7.5% EFdA/LNG PGSU



2.4 x 40 mm



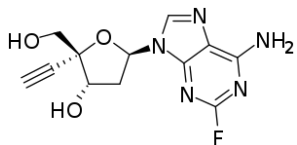
PBS, pH 7.4, 37°C



# Multi -purpose Prevention Technology (MPT) Implants

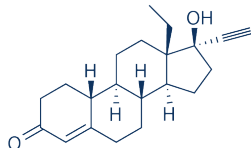
BILL & MELINDA  
GATES foundation

Calibr  
at Scripps Research



EFdA

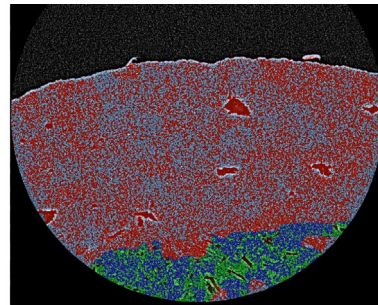
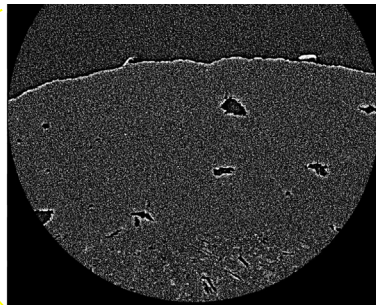
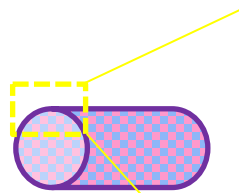
Solubility in dissolution  
media = 900 µg/mL



Levonorgestrel

Solubility in dissolution  
media = 6 µg/mL

40/15% EFdA/LNG PGSU



Post-release Pore | API | Polymer



55% LNG PGSU

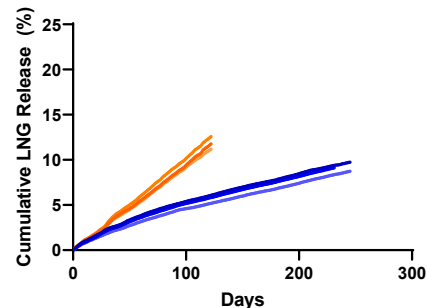
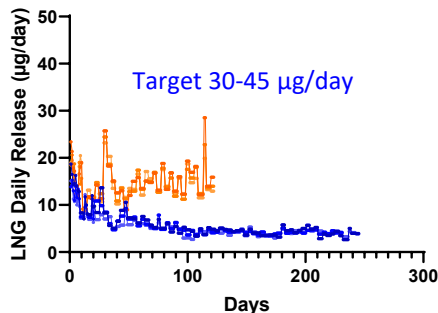


1.1 x 20 mm

55% LNG PGSU



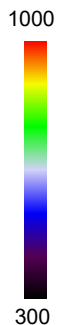
0.6 x 30 mm (x3)



PBS, pH 7.4, 37°C

# Ocular Micro -scale Implants

Raman PAT for Content Uniformity



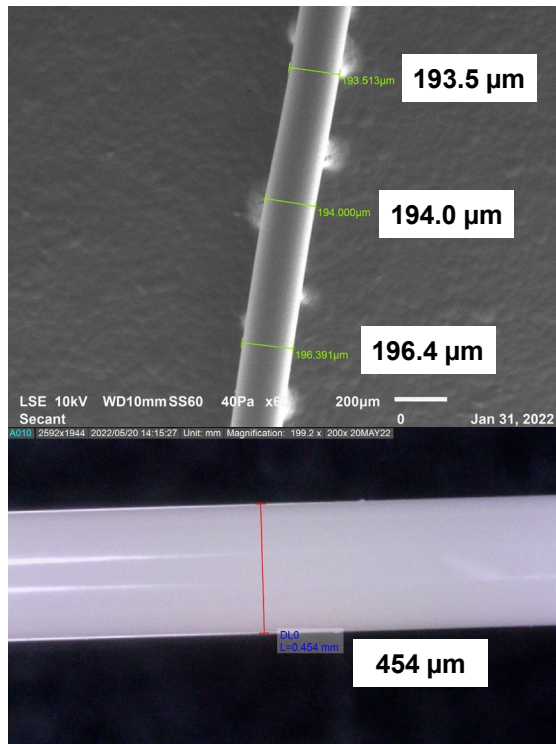
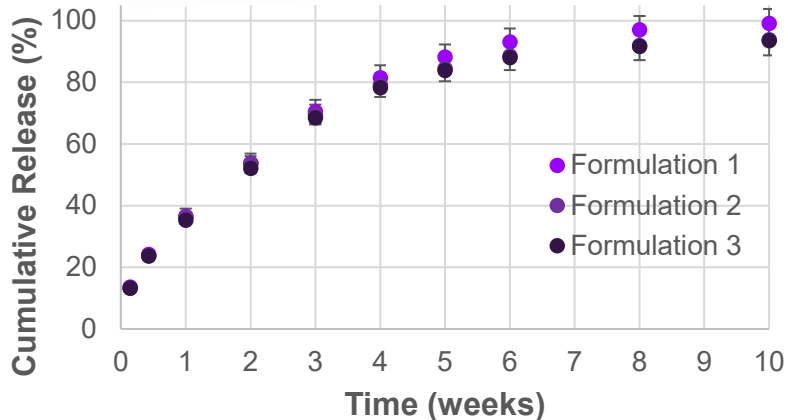
Formulation 1



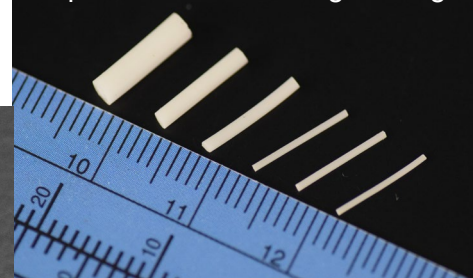
Formulation 2



Formulation 3

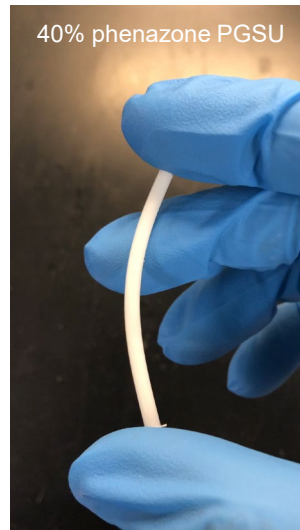
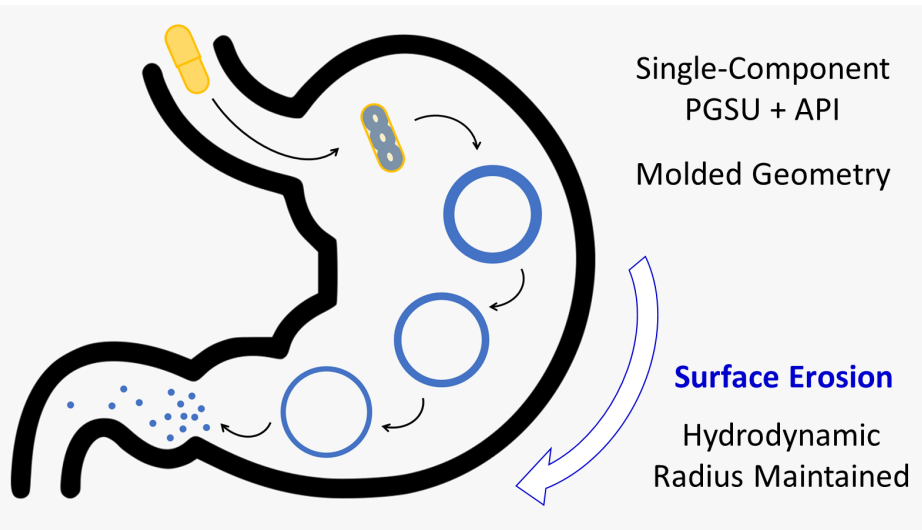


Up to 70% & 80% drug loading



Administered via 17G to 27G

# Gastroretentive Oral Dosage Forms



PGSU traits:

- 1) elastomeric
- 2) biodegradable
- 3) controlled release

Total payload up to 700mg of API

# Preclinical Proof of Concept

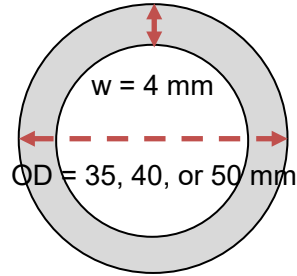
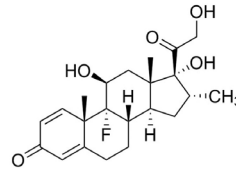
## 30% Dexamethasone with 5% BaSO<sub>4</sub> PGSU Rings

Design 1 1 x 4 x 35 mm: 500 mg Ring  
150 mg Dexamethasone/Ring

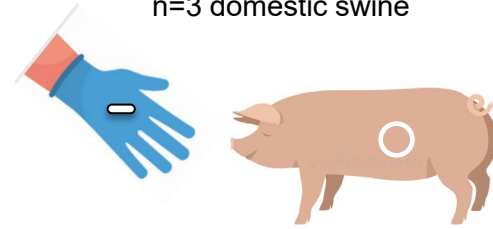
Design 2 1.5 x 4 x 40 mm: 880 mg Ring  
265 mg Dexamethasone/Ring

Design 3 1.5 x 4 x 50 mm: 1086 mg Ring  
325 mg Dexamethasone/Ring

 t = 1 or 1.5 mm



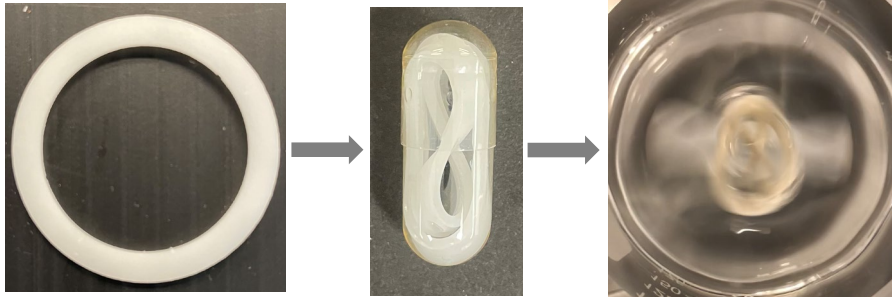
n=3 domestic swine



n=5 beagle dogs

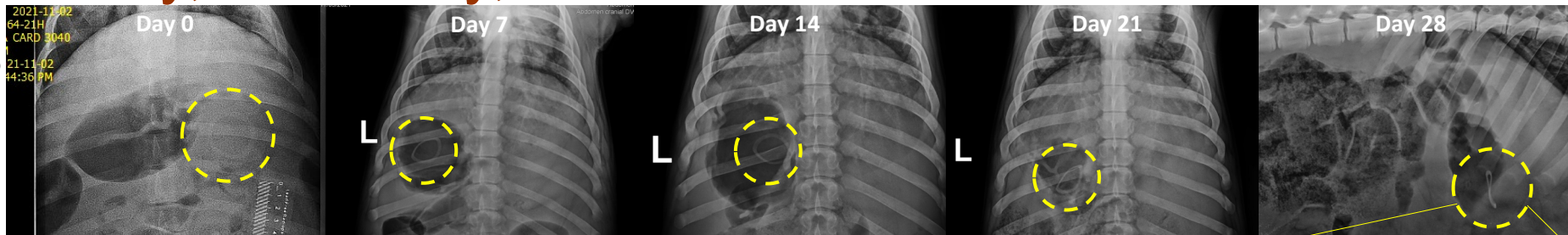


n=5 beagle dogs

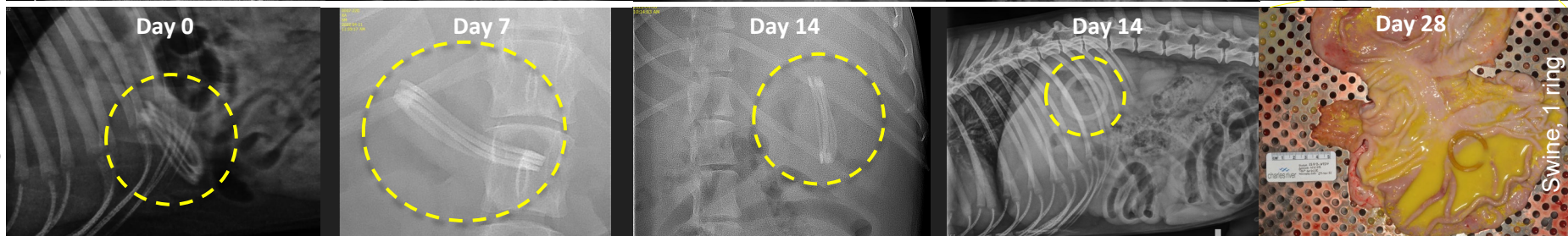


# Safety, Tolerability, & Retention

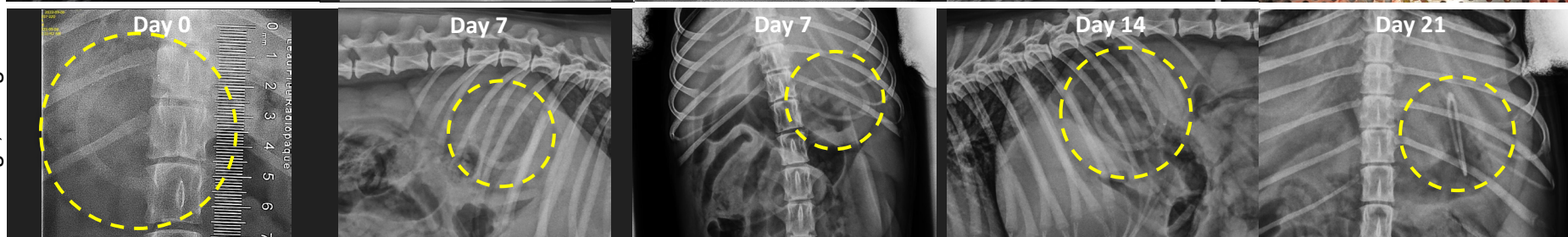
Swine, 1 ring



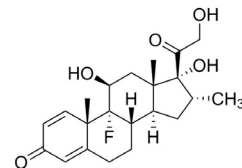
Dogs, 3 rings



Dogs, 1 ring

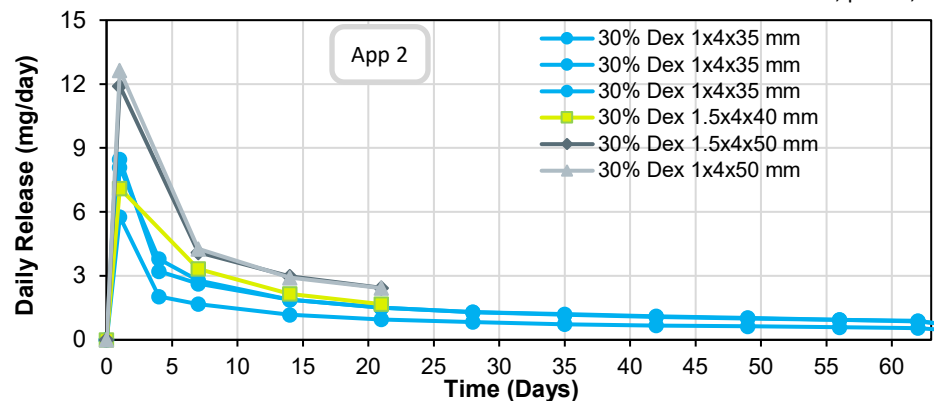
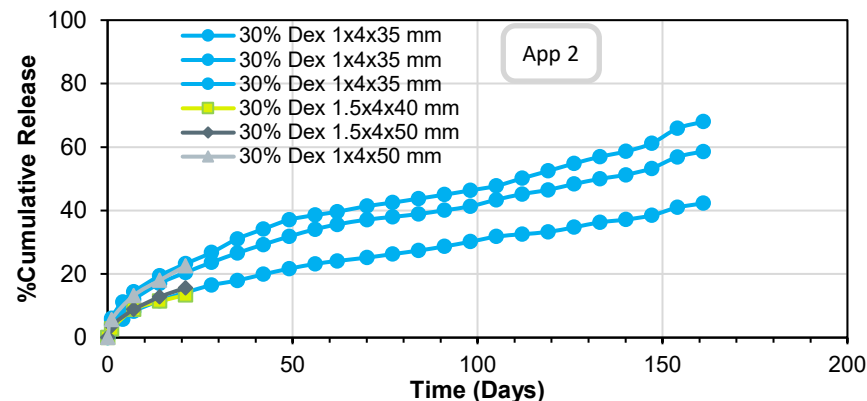
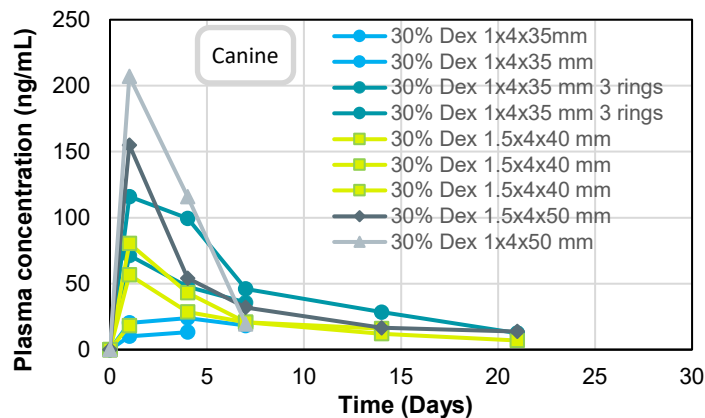
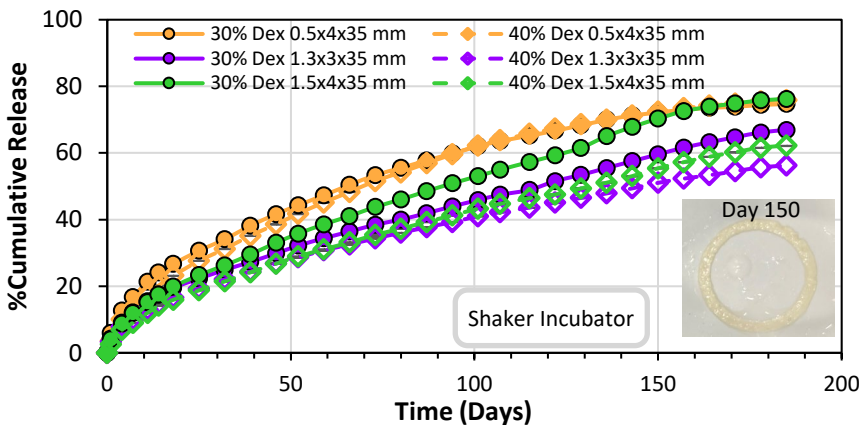


# In Vitro - In Vivo Correlation



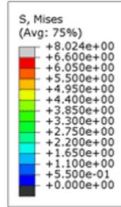
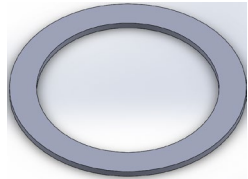
Solubility in dissolution media = 75 µg/mL

SGF, pH 1.2, 37°C

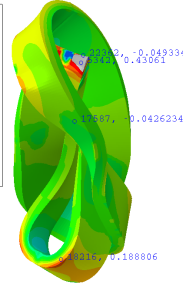
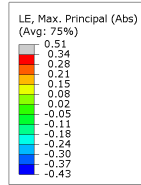


# Finite Element Analysis for Shape Optimization

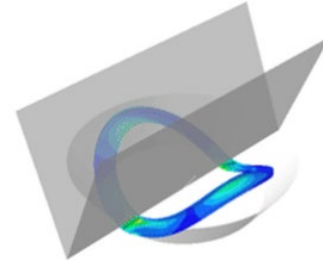
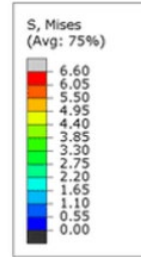
Folding in Capsule



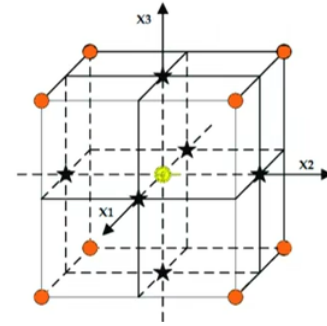
Relaxation in Capsule



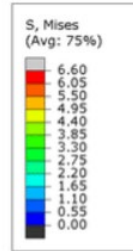
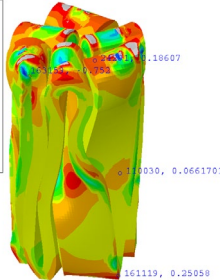
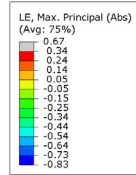
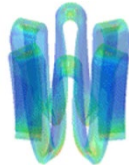
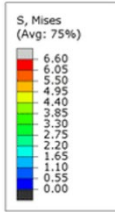
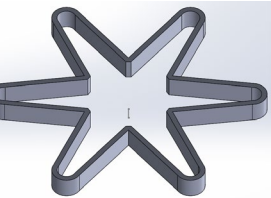
Resistance to Pass through Pyloric Sphincter



DOE



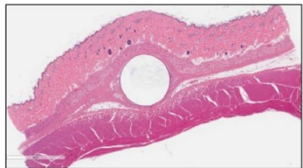
- Centre Points
- Factorial Points
- ★ Star Points





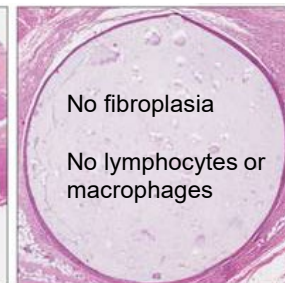
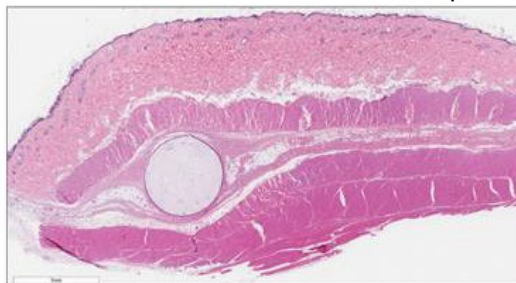
# Preclinical Studies

3mo subcutaneous implantation, rat



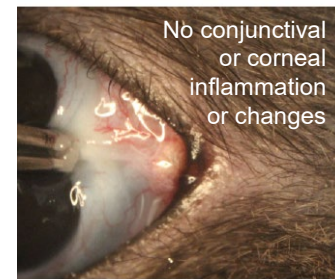
Minimal fibroplasia  
No lymphocytes or macrophages

8mo subcutaneous implantation, rat



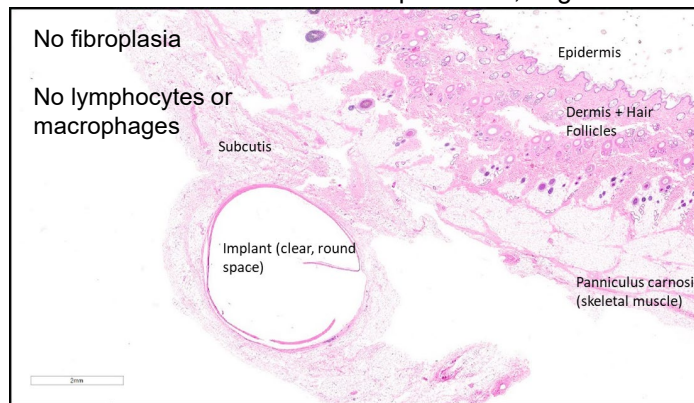
No fibroplasia  
No lymphocytes or macrophages

4wk episcleral implantation, rat



No conjunctival or corneal inflammation or changes

6mo subcutaneous implantation, dog



No fibroplasia

No lymphocytes or macrophages

Epidermis

Dermis + Hair Follicles

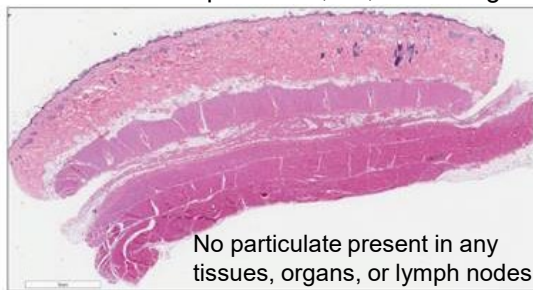
Subcutis

Implant (clear, round space)

Panniculus carnosus (skeletal muscle)

- ❑ Small, medium, and large animal testing
- ❑ Subcutaneous, intravitreal, episcleral, and oral dosing
- ❑ Full extractables & leachables characterization

3mo subcutaneous implantation, rat, 100% degradation



No particulate present in any tissues, organs, or lymph nodes

# Biocompatibility

## USP Class VI Testing

ISO 10993 Test	Scoring
Cytotoxicity	0/0/0
Irritation: Intracutaneous Injection	0/0, 0/0, 0/0, 0/0, 0/0
Systemic Toxicity: Systemic Injection	0/0/0/0/0
Implantation: Intramuscular 1 week	0/0

## Biodegradation & Toxicity Assessment

PGSU Monomer	Biodegradant Species	Biodegradation Pathway
Glycerol	Dihydroxyacetone phosphate Glyceraldehyde 3-phosphate	Metabolized by Glycolysis, Gluconeogenesis
Sebacic acid	Acetyl-coA Succinyl-coA	Metabolized by Citric acid cycle
Hexamethylene diisocyanate	Hexamethylene diamine CO2 Ureas	Excreted in Urine, Breath
Tin(II) 2-ethylhexanoate	2-ethylhexanoate Tin(II)	Excreted in Urine

## Full ISO 10993 Testing

ISO 10993 Test	Scoring
Cytotoxicity	0/0/0
Irritation: Intracutaneous Injection	0/0, 0/0, 0/0, 0/0, 0/0
Systemic Toxicity: Systemic Injection	0/0/0/0/0
Systemic Toxicity: Material Mediated Pyrogen	0/0/0
Hemocompatibility: Complement Activation	Like negative control
Hemocompatibility: Partial Thromboplastin Time	Like negative control
Hemocompatibility: Platelet & Leukocyte Count	Like negative control
Hemocompatibility: Hemolysis	Like negative control
Genotoxicity: Ames	Like negative control
Genotoxicity: Chromosomal Aberration	Like negative control
Sensitization	Like negative control
Implantation: Subcutaneous 4 week	0/0/0, no reaction
Implantation: Subcutaneous 6 month	0/0/0, no reaction
Implantation: Subcutaneous 12 month	0/0/0, no reaction

# Technology Readiness

 **Chemistry, Manufacturing, Controls**

- Analytical method development & validation
- Equipment for manufacturing at scale

 **Stability**

- Room temperature/humidity storage stable for 3 years
- Long-term, accelerated, & thermal cycling per ICH Q1A

 **Biocompatibility**

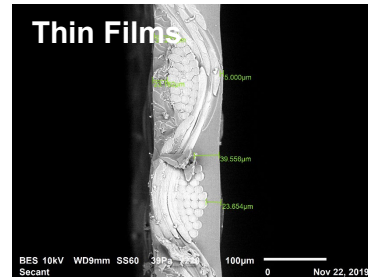
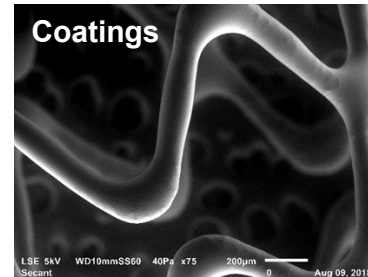
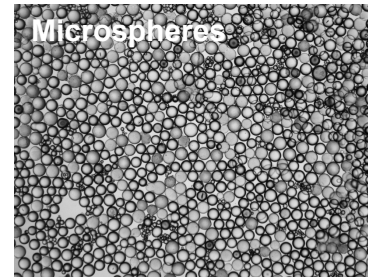
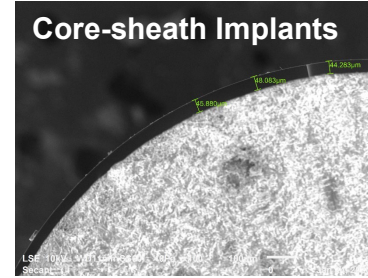
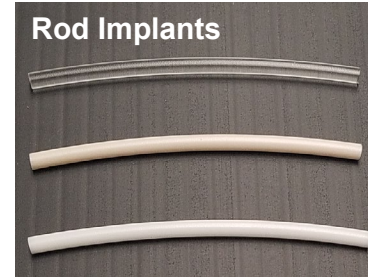
- No chronic inflammation, no fibrous encapsulation
- USP Class VI, ISO 10993, including 6- and 12-month implants

 **Sterilization**

- Stable to 18-29 kGy and 25-34 kGy gamma irradiation
- Electron beam and ethylene oxide possible

 **Regulatory Status**

- Type IV DMF on file with FDA as of Jan 2022
- MAF with FDA, CE Mark in EU, 510k submitted March 2022



# The Value of Partnership

