

# 長期徐放性ドラッグデリバリー (DDS) 用ポリマー

## DSM's innovative polymer platforms for application in long acting drug delivery systems

Solving unmet needs in sustained delivery

CPhI Japan – Drug Delivery Systems

November 2020



**DSM**

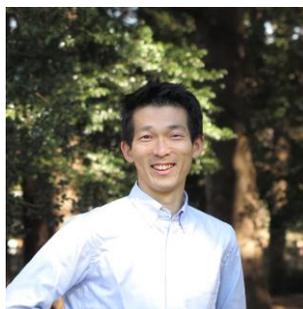
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# 講演概要

長期徐放性を有するポリマー（臨床応用実績あり）として、生分解性PolyEsterAmide (PEA) および非分解性ポリウレタンを展開する。PEAでは様々なAPI（低分子化合物 - キナーゼ阻害剤、peptide - GLP-1受容体作動薬、protein）を用いた数ヵ月間のin-vitro長期徐放プロファイルについて説明します。また避妊リングなどに実績のある脂肪族ポリウレタンも紹介します。



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Your Business Network



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# DSM at a glance

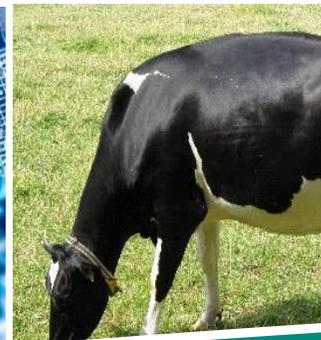
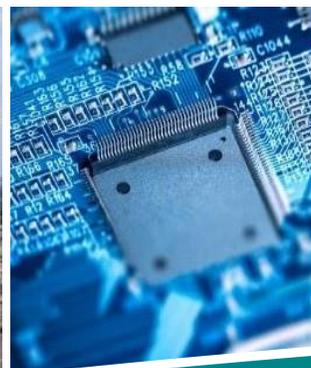
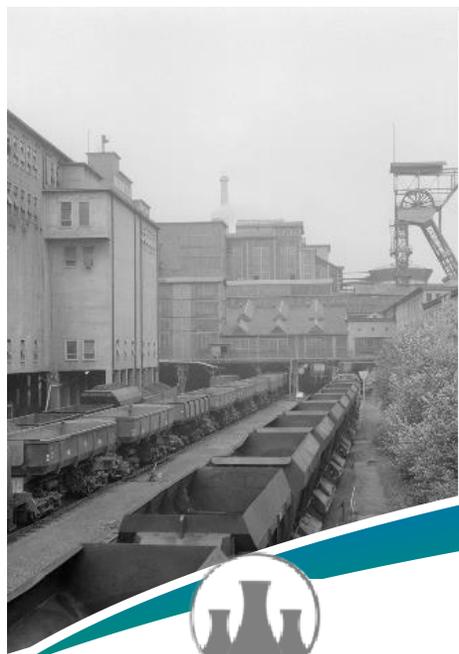
*Purpose-led science to address  
the world's challenges in nutrition,  
health and sustainable living*

# 百十数年の歴史を通して事業を大きく変化 Successful transformation future-proofing DSM

炭鉱  
Coal mining

基礎・石油化学  
(Petro)chemicals

栄養、健康、持続可能な分野  
Nutrition, Health & Sustainable Living



2018

1902



1950~

**DSM**



1970~

*Unlimited.*

**DSM**

2000~



**DSM**



# DSMにとっての主要市場

売上 約一兆円

マテリアル

パッケージング

スーパー  
繊維



食品・飲料

乳幼児  
栄養食品



サプリメント



パーソナルケア

ニュートリション

畜産飼料



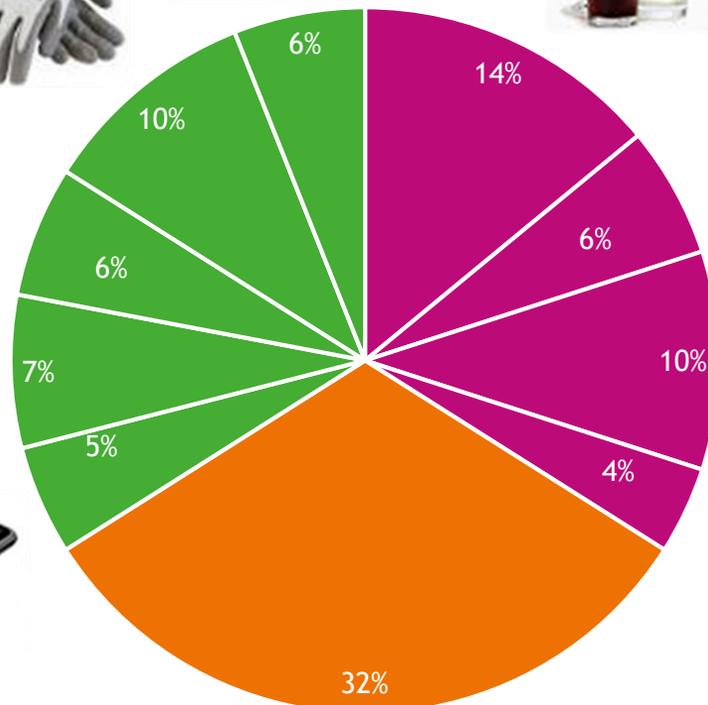
住宅・建設



自動車



電気・電子

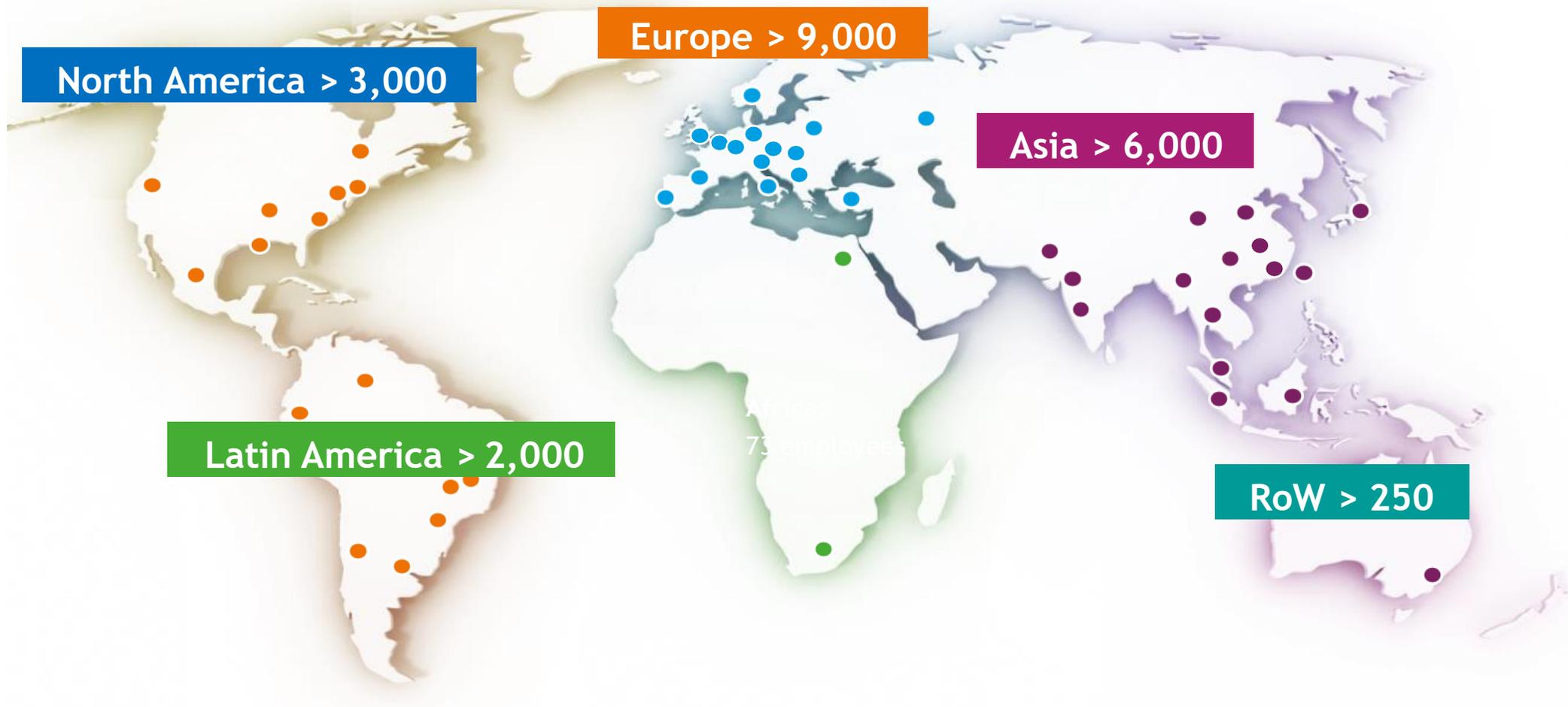


# DSMの世界展開

## DSM global workforce

~60% Employees outside Europe (2018) VS. 37% in 2006

~23,000 Employees incl. JVs/associates



# 弊社関連記事や本

**日本経済新聞** 朝刊・夕刊 ストーリー Myニコ

トップ 速報 マネー 経済・金融 政治 ビジネス マーケット テクノロジー 国際 オピニオン スポーツ 社会・く

## SDGsはもうからない？ 蘭DSMはなぜ稼げるのか

[SDGs コラム \(テクノロジー\)](#)  
2020/9/14 2:00 | 日本経済新聞 電子版

保存 共有 他

「それで、いくらもうかるんだ？」——。持続可能な開発目標（SDGs=エスディーゼー）への取り組みの必要性を説明する社員に、ある日本企業の経営者が発した言葉だ。もう何年もこの状況が変わっていない。

ご存じの通り、SDGsは持続可能でより良い世界をつくることを目指す国際目標である。2015年9月の国連サミットで採択されたもので、30年を年限とする17の国際目標（ゴール）が設定された。現在、SDGs…

この記事は会員限定です。電子版に登録すると続きをお読みいただけます。

無料・有料プランを選択 会員の方はこちら

今すぐ登録 ログイン

Sustainability 「未来市場」のつくり方

サステナビリティで変わる企業の常識

DSM(株) 代表取締役社長 中原雄司 [著]

東洋経済新報社

図解入門 ビジネス Shuwasystem Business Guide Book How-nual

最新

# SDGsの手法とツールがよ〜くわかる本

サステナブルなビジネスをするために

## 優先課題の特定から情報開示までの行程がわかる!

- SDGsの本質や構造、仕組みがわかる!
- 優先課題や具体的な行動がわかる!
- 目標設定のステップとツールがわかる!
- SDGs情報を開示する方法がわかる!
- 先進企業の取り組み事例がわかる!

天沼 伸恵 / 小野田 真二 編著 秀和システム

<https://www.nikkei.com/article/DGXMZO63332260S0A900C2000000/>

# DSM Biomedical

## Our Vision

Solving our world's healthcare needs  
through sustainable science

*A division of Royal DSM*

Exton, PA  
Geleen, The Netherlands  
Berkeley, CA  
Greenville, NC  
Shanghai, China  
Tokyo, Japan



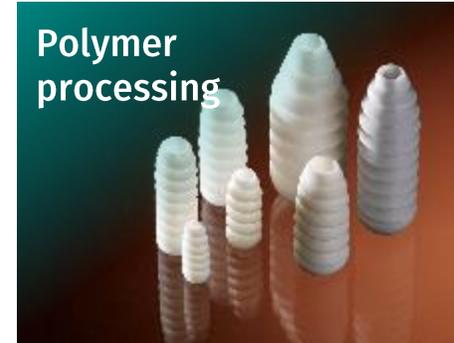
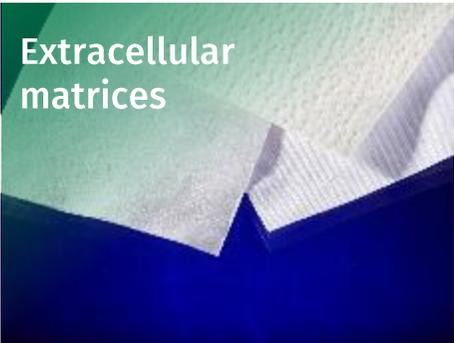
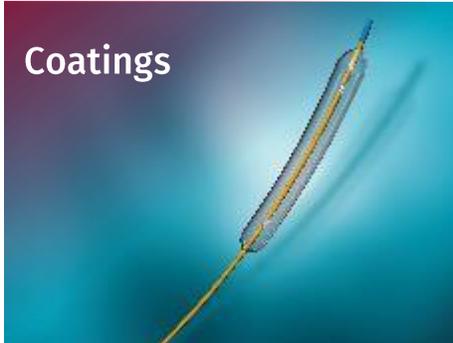
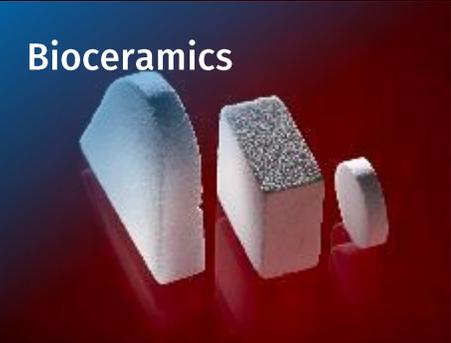
# Global presence

*~450 employees*



# Broadest portfolio of biomaterial solutions

*Supported by a solid science foundation*



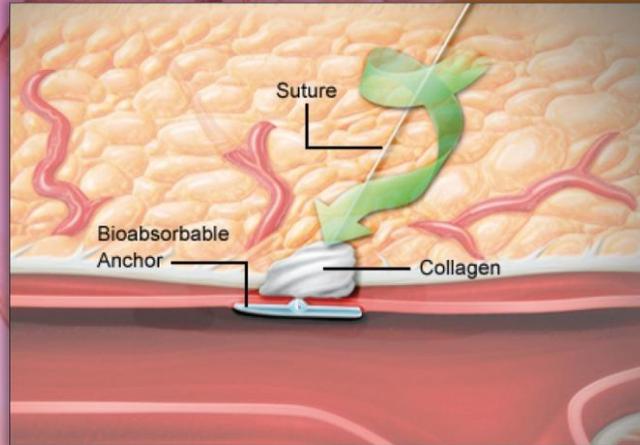
# DSM has a solution to assist patients undergoing a catheterization procedure

## Collagen solutions for puncture closure

Uniquely formulated collagen provides rapid but safe hemostasis after cardiac procedure



Terumo's Angio-Seal™ Vascular Closure Device



> 2-million patients annually

Reduction in hospital stay time

Remodels quickly leaving nothing in patient

# DSM has a solution to help treat rheumatic heart disease

## Polyurethane solutions for heart valves

CarboSil® TSPCU gives the valves durability and also dispenses with the need for anticoagulants



Strait Access Technologies (SAT) Heart Valve

30+ years of  
clinical history

7 master file  
families at FDA

Tailored surface  
properties

# Innovative technologies for sustained drug delivery

NUTRITION · HEALTH · SUSTAINABLE LIVING



**DSM**

BRIGHT SCIENCE. BRIGHTER LIVING.

We enable product innovation in sustained drug delivery with the development of customized solutions with tunable properties to suit the active pharmaceutical ingredient (API), the physiology of the delivery site, and the desired target profile of the end-product.



NUTRITION · HEALTH · SUSTAINABLE LIVING



**DSM**

BRIGHT SCIENCE. BRIGHTER LIVING.

# Why sustained delivery?

To enable improved clinical outcomes & patient compliance, to realize better healthcare economics, and to significantly reduce medical waste



## Product examples utilizing DSM Technology

Ophthalmic injectable designed for 6-month application (Phase 1 clinical, treatment of AMD & DME) – Once every 6 months vs Once every 4-6 weeks



Diabetes management implant designed for 6-month delivery of GLP-1 RA (in development) – Once every 6 months vs once daily / weekly



- Estimated reduced use\* of surgical gloves by >40 tons per year
- Over \$3M per year saving in disposables use
- Estimated reduced use\* of injectors
  - by 3M per year with 20% market adoption
  - by 12M per year with 100% adoption (US only)



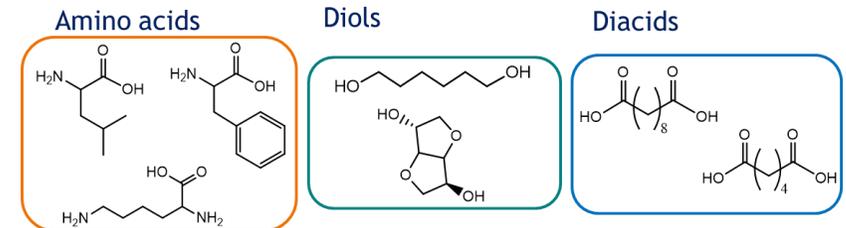
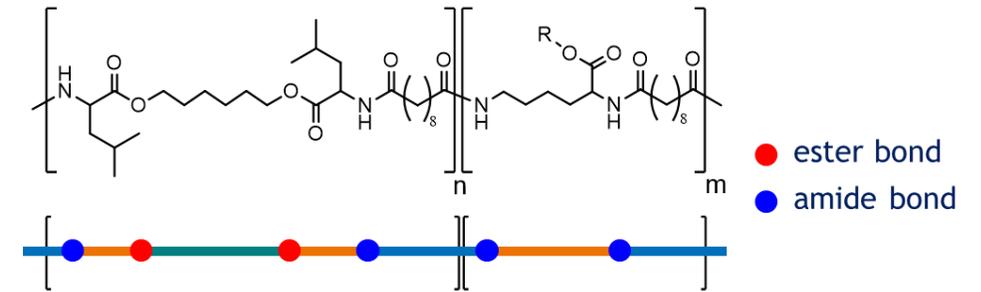
# DSM Biomedical Drug Delivery

*Polymer platforms for application in injectable and implantable long acting drug delivery systems*

- **Biodegradable PolyEsterAmides (PEAs)**
  - Proven innovative biodegradable materials for sustained drug delivery application
- **Biostable Thermoplastic PolyUrethanes (TPUs)**
  - Customizable & proven biostable platform for sustained drug delivery applications

# PolyEsterAmide technology – a proven biodegradable material platform solution for sustained drug delivery

- Broad compatibility with wide range of small molecule and biological drugs due to low susceptibility to acylation (i.e., interaction of polymer with API's nucleophilic primary amines)
- Excellent biocompatibility proven in multiple settings including ophthalmic, intravascular, intra-articular applications
- Near linear release from weeks to greater than 6 months\*
- Controlled degradation kinetics (weeks to multiple months); no acidification of micro-environment; no bulk degradation preventing irregular biphasic release kinetics; surface erosion allows for implant removability\*\*
- Unique solubility properties (incl. low hydrocarbon alcohols) provides for ease of processing with active pharmaceutical ingredients incl. low temperature melt processing into multiple product forms (fibers, microparticles, films, foams, coatings)
- Broad IP protection provides opportunities for lifecycle extension



DSM offers polymer solutions tailored to sustain drug elution over the lifetime of the implant, while allowing ease of processing with active pharmaceutical ingredients.

\* polymer-drug formulation dependent  
\*\* in case of adverse reactions for example; shape and time-dependent

# PEA application examples



## **Svelte Medical Systems Announces CE Mark Certification of SLENDER IDS™**

***The World's First Drug-Eluting Coronary Stent-on-a-Wire Integrated Delivery System Downsizes Catheters, Facilitates Transradial Intervention (TRI) and Maximizes Procedural Efficiency***

- Approved in EU, US & Japan expected
- PEA III AcBz used as drug eluting stent coating



## **Aerie Pharmaceuticals, Inc. and DSM Biomedical, Inc. Expand Collaboration Agreement Focused on Novel Drug Delivery Technology in Ophthalmology**

August 1, 2018

**Promising Technology Platform to Potentially Deliver Therapies to Treat a Broad Spectrum of Ophthalmic Diseases**

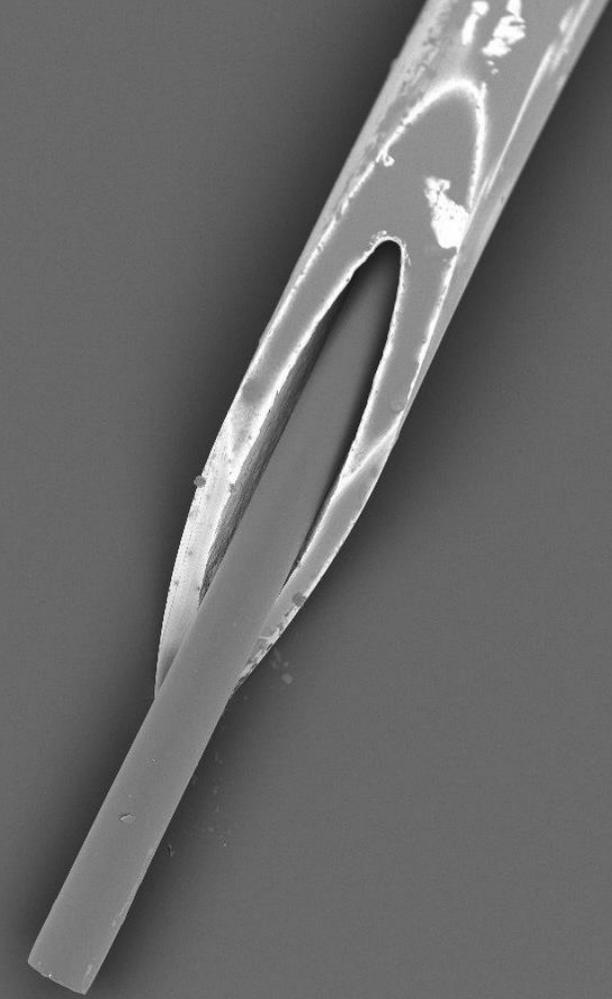
DURHAM, NC & EXTON, Pa.--(BUSINESS WIRE)--Aug. 1, 2018-- Aerie Pharmaceuticals, Inc. (NASDAQ:AERI), an ophthalmic pharmaceutical company focused on the discovery, development and commercialization of first-in-class therapies for the treatment of patients with open-angle glaucoma, retina diseases and other diseases of the eye, and DSM Biomedical, Inc., a global solutions provider in biomedical science and regenerative medicine, today reported that they have expanded their collaborative research, development, and license agreement.

- Phase 1 Clinical Trial
- 6-month sustained release application
- Exclusive PEA license in Ophthalmology
- New generation PEA III X as API carrier

# PEA / Form Compatibility

## *Long Acting Injectable Fibers & Rods*

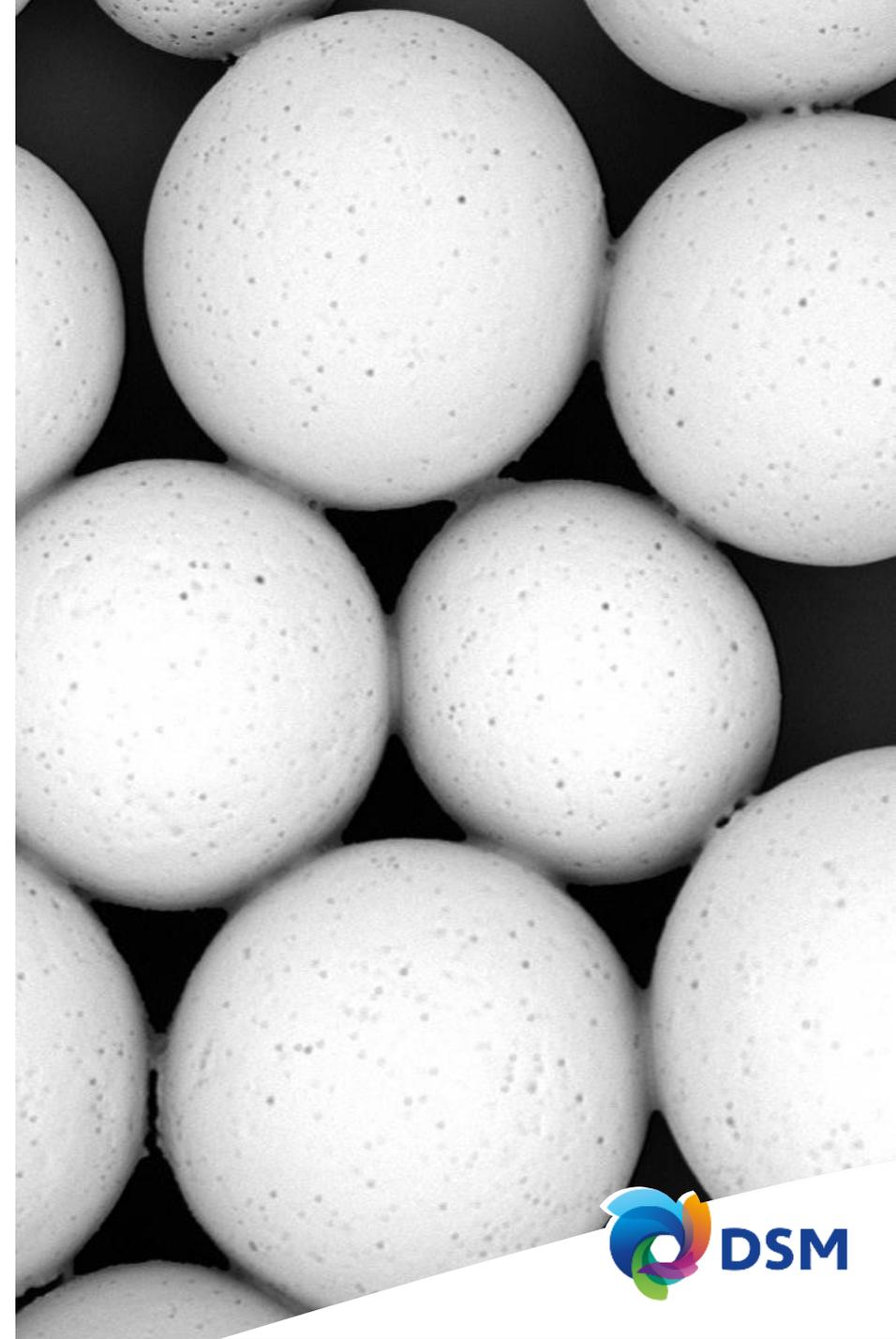
- Typical Specifications:
  - Diameter 200 $\mu$ m – mm
  - API loading 5% – >50% w/w
  - Injectable - 27G (200 $\mu$ m implant) – 12G (2mm implant)
  - **No stitching required**
- Processing Options:
  - Extrusion & Injection Molding
  - Low temperature processing techniques
  - Small Batch processing possible
- **PEA fiber currently in Phase 1 clinical trial**



# PEA / Form Compatibility

## *Long Acting Injectable Micro Particles*

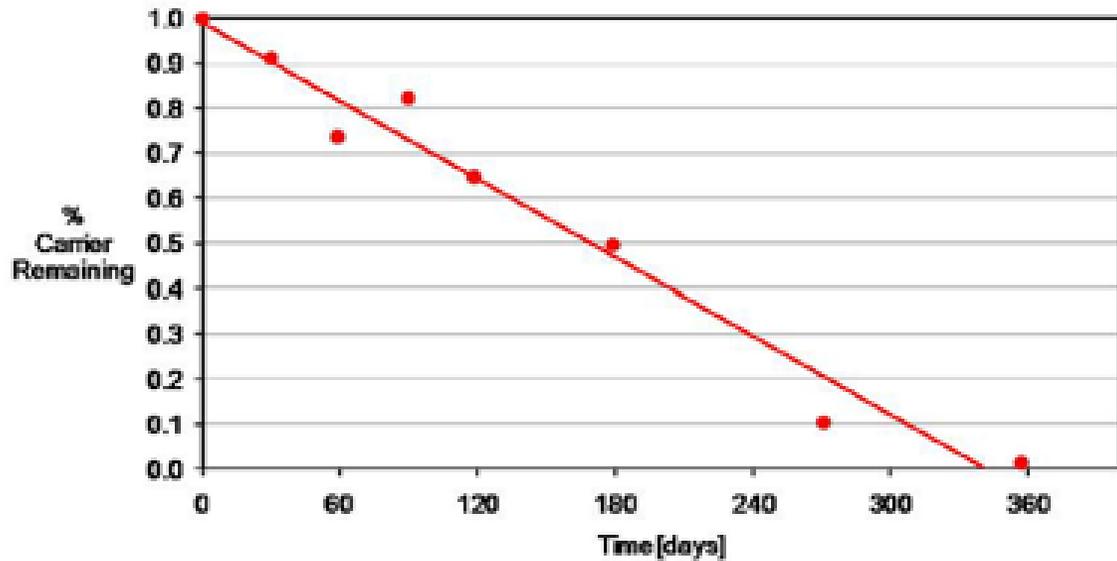
- Typical Specifications:
  - Diameter ~10 $\mu$ m - 100 $\mu$ m
  - Injectable - 30G (10 $\mu$ m MPs) – 23G (10 $\mu$ m MPs)
  - API loading 5%-30% w/w
- Processing Options:
  - Numerous methods available – emulsification, spraying...
- **Long Acting Efficacy proven in pre-clinical studies**
  - Proven superiority of PEA MicroParticle formulation vs PolyEster based commercial product - superior efficacy in in chronic disease animal model\*



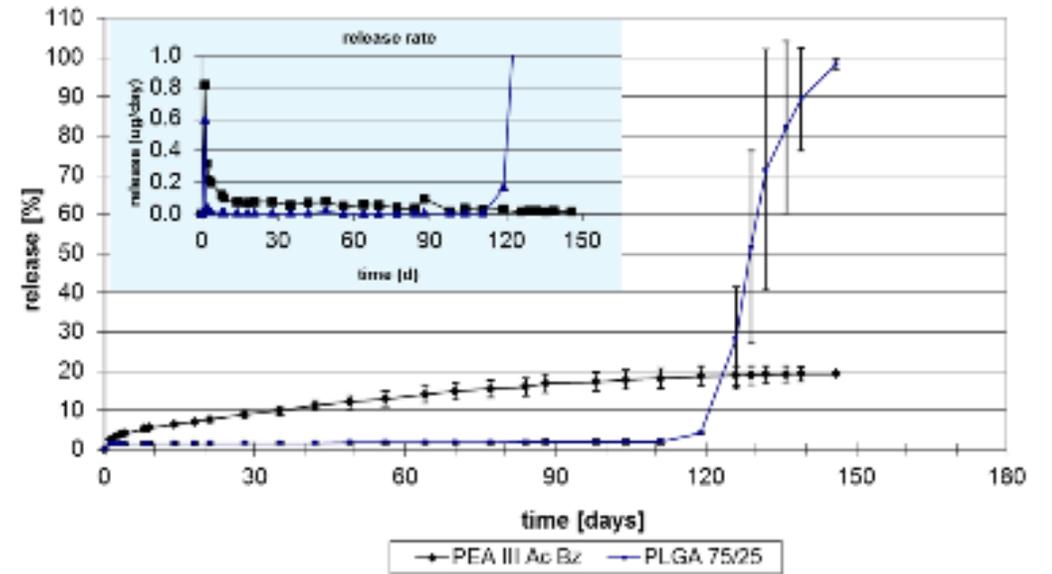
# PEA / Form Compatibility

## Coatings

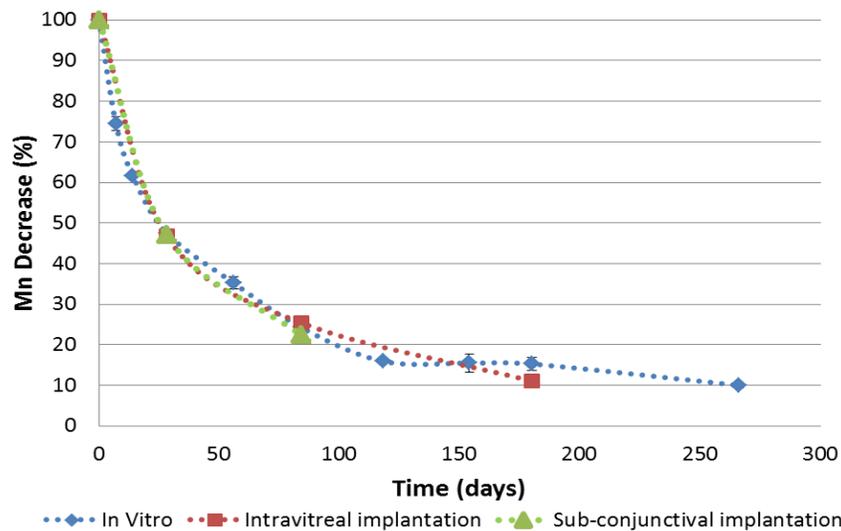
- Compatibility with number of substrates
- Excellent adhesion to metals
- Processing Options
  - Excellent melt processability
  - Solutions processability
  - Unique solubility properties
- **PEA coating in commercial product – Sirolimus eluting coating on Drug Eluting Stent\***



Controlled, multiple months degradation profile – size/ API/ application dependent



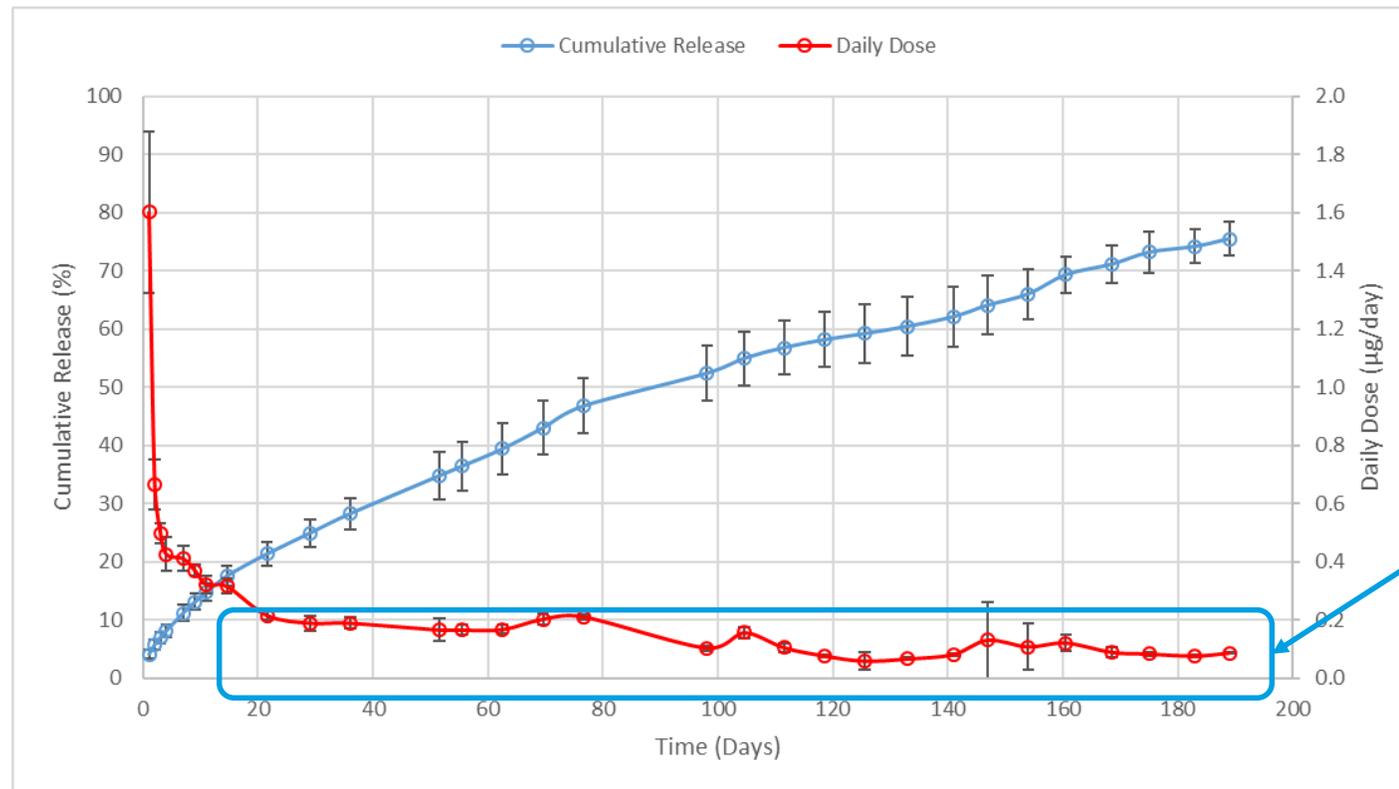
No bulk degradation, no acidification of micro-environment, lack of secondary burst / disintegration of the implant



Good correlation in-vitro and in-vivo up to 180 days

# Sustained delivery of a commercial Kinase Inhibitor (KI) Challenge: Polymer Compatibility with Free Amine APIs\*

*In-vitro >6-month sustained release*



## Form details

- Injectable micro-Fiber
- 100µg total weight
- 40µg total API load

## Results

- 6+ month release
- Near Zero-Order (80-200ng/day)

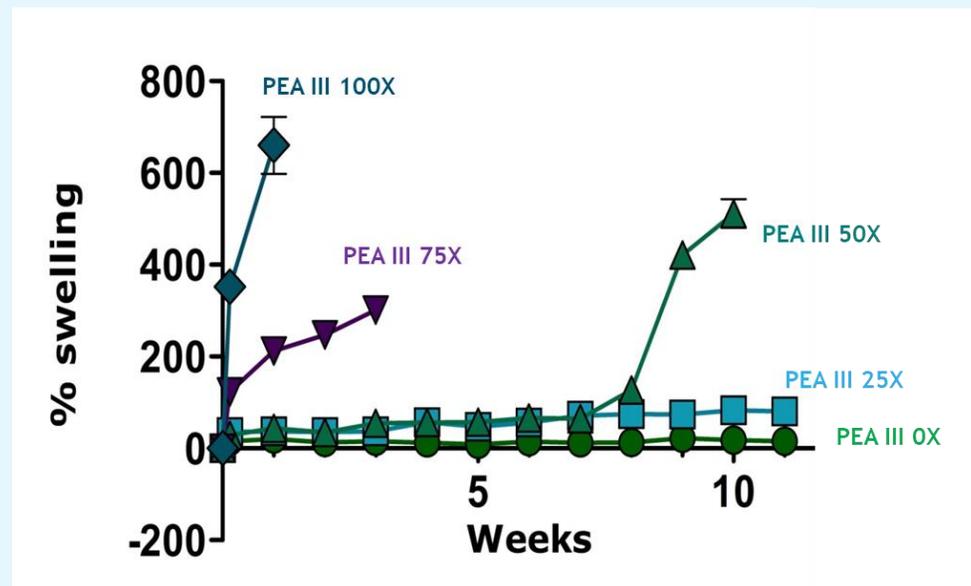
\*Formulation / processing of free amine APIs with PolyEsters typically results in disintegration of polymer in 2-7 days

# Sustained delivery of biologics

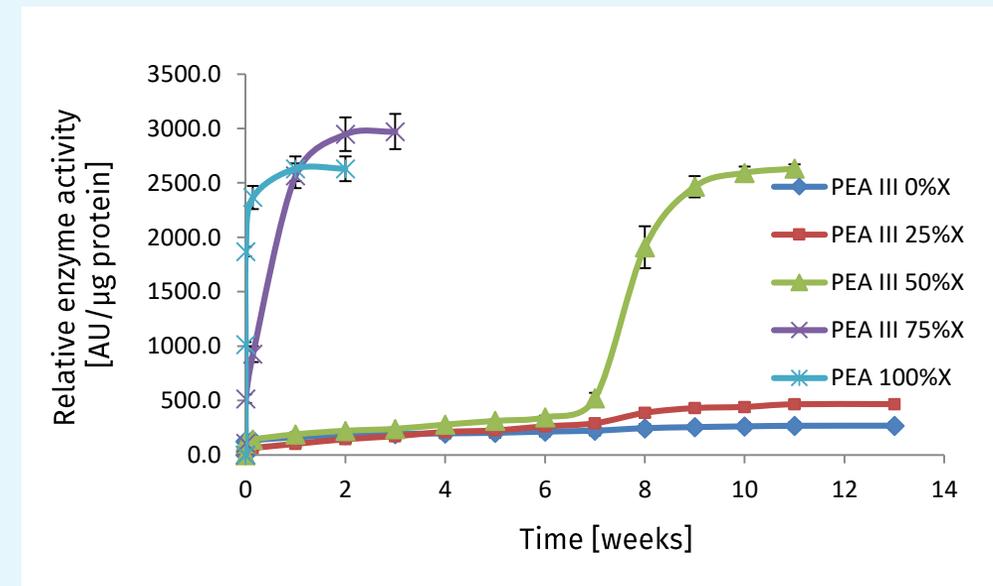
## Challenge: Diffusion of large molecules from polymer

*Full retention of bioactivity of horseradish peroxidase (44kDa)*

### Controlled Degradation & Swelling



### Release of HRP with Retention of Bioactivity



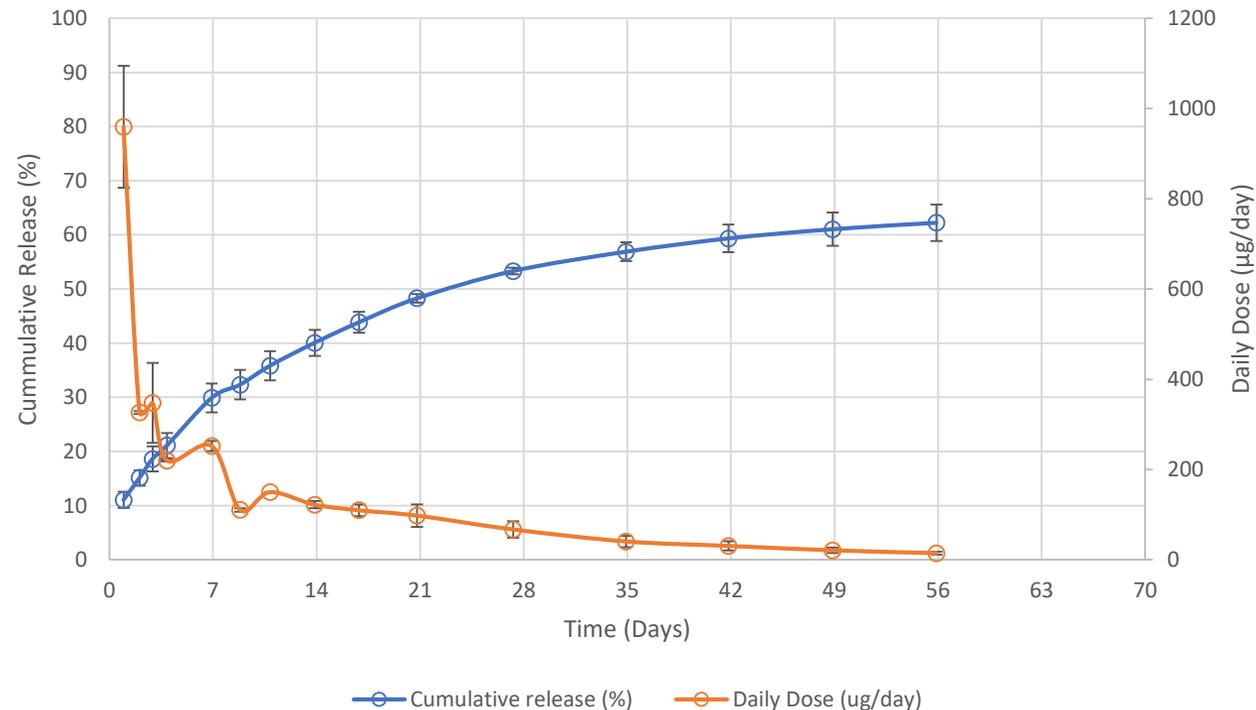
**Intrinsic properties of PEA: Lack of degradation-associated acidification of microenvironment contributes to preserving of HRP bioactivity**

# Sustained delivery of GLP-1 Receptor Agonist

## Product concept interim results

*Sustained release & full bioactivity retention of GLP-1 RA*

**GLP-1 RA in-vitro release from 30% w/w GLP-1 RA PEA rod (2mm x 10mm)**



### Cell based results (Path Hunter Activity Test)

- Full retention of bioactivity of GLP-1 RA post process
- Full retention of bioactivity of GLP-1 RA extracted from implant after 6 weeks of in-vitro release
- Retention of bioactivity of released GLP-1 RA

### We are advancing leading formulation into in-vivo evaluation stage:

- Intravenous glucose tolerance test + oral glucose tolerance test - efficacy data benchmarked against an acute injection
- Tolerability study - focus on subQ route
- PK study benchmarked against an acute injection

# DSM Biomedical Drug Delivery

*Polymer platforms for application in injectable and implantable long acting drug delivery systems*

- **Biodegradable PolyEsterAmides (PEAs)**
  - Proven innovative biodegradable materials for sustained drug delivery application
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# Proven Biostable polymer platform for sustained drug delivery

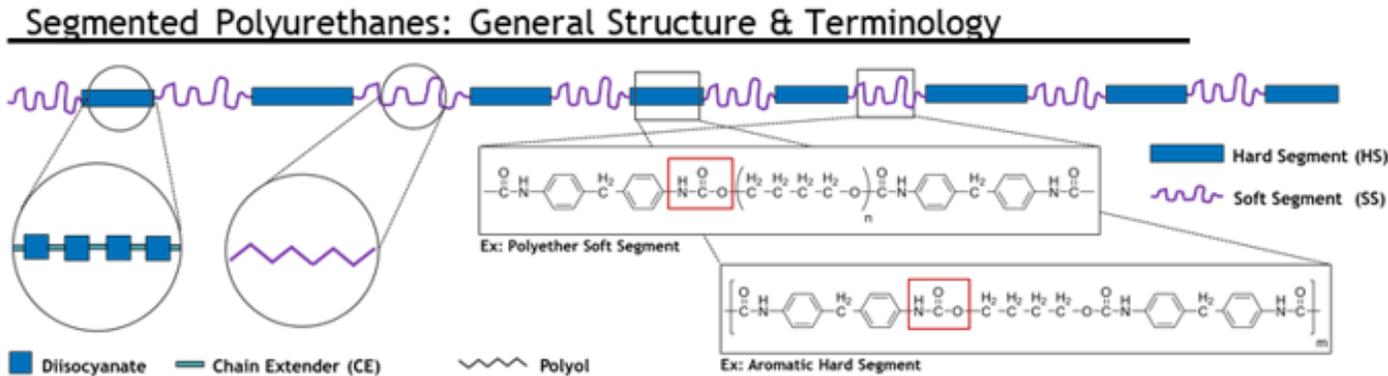
## *Polyurethane Technology*

- ✓ Proven clinical history
- ✓ **Material Master Files on file with the FDA / GMP manufacturing**
- ✓ **Capability to customize** for specific hydrophobicity / hydrophilicity, time duration in body, desired elution rates, hardness/loading capacity, and processing parameters (ex. Impact of API degradation temp)
- ✓ Available support from feasibility to development/implementation
- ✓ Melt processing know how backed by an extensive global scientific community for additional partner support
- ✓ **Polyurethane technology provides a customizable, biostable platform for sustained pharmaceutical delivery applications**



# Biostable Polymer - Polyurethane Structure

*Sustained delivery in implantable applications*

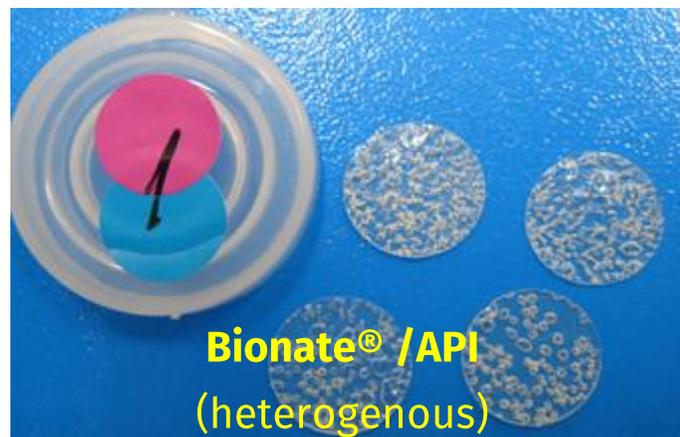
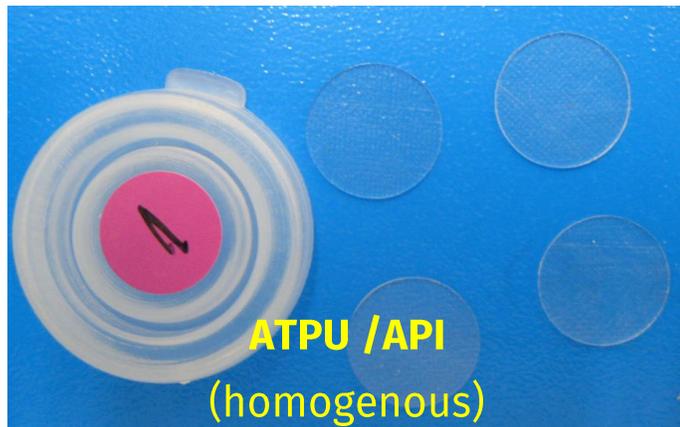


- DSM offers multiple biostable polymers for use in sustained delivery applications
- The diversity in chemical structures of PUs and the possibilities to do functional modifications make them eligible as controllable devices of low molecular weight drugs as well as biotherapeutics.
- A desired profile of release can be tailored by controlling the hard/soft segment ratio, hydrophilicity of the soft segment and using ionic interactions between the polymer segments and drugs.
- Enabling possibility of low temperature melt processing
- Mechanical properties suitable for flexible applications

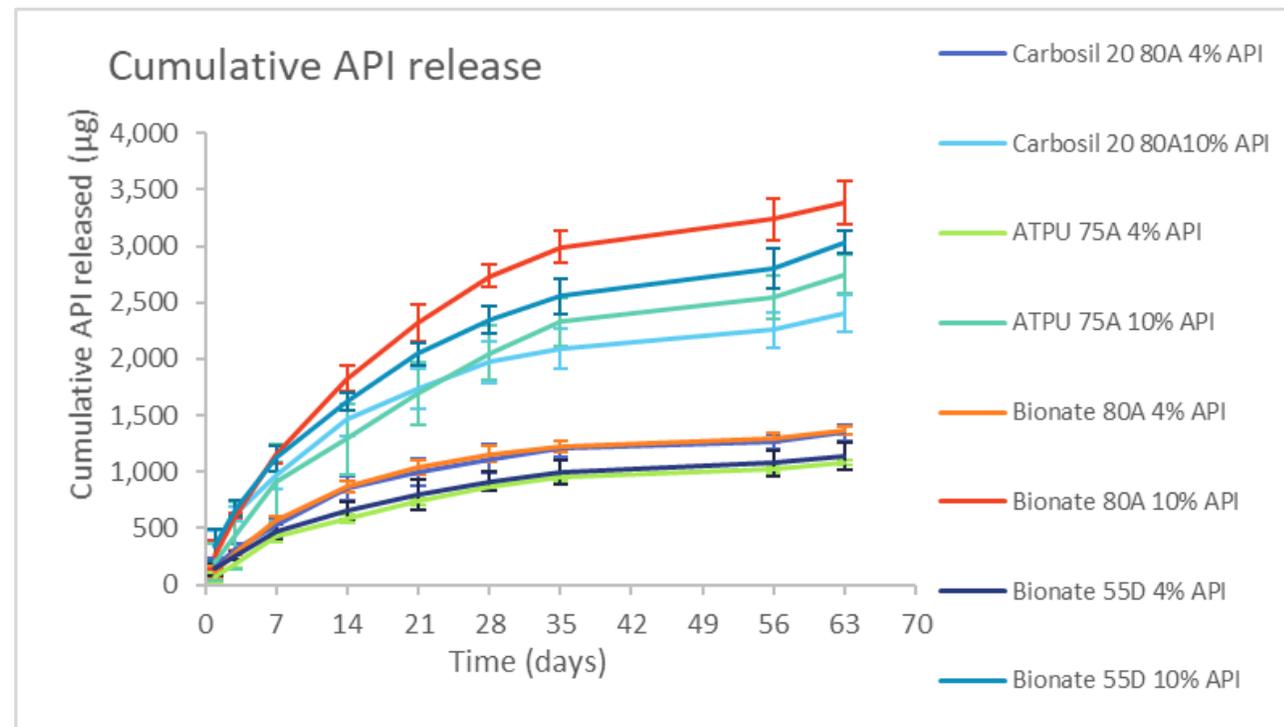
# Biostable Polymer Platform

*Tunable solutions via multiple material choices and custom formulation approach*

- Choice of different TPU material results in different type of formulation (same API)



- Tunable release profile based on material and choice and formulation approach



# Sterilization Evaluation

*No impact noted on base DSM polymers after sterilization*

In order to evaluate the impact of sterilization on its materials, DSM conducted an assessment of selected polyurethanes in its portfolio.

**No loss in strength** at stress at 5% elongation (see Figure 1) was observed when exposed to EtO sterilization in accordance with ISO 11135 – Sterilization of Healthcare Products

**No loss of strength** at 5% elongation (see Figure 1) was observed when exposed to gamma irradiation up to 45 KGray (1 Gray = 1 Joule/Kg).

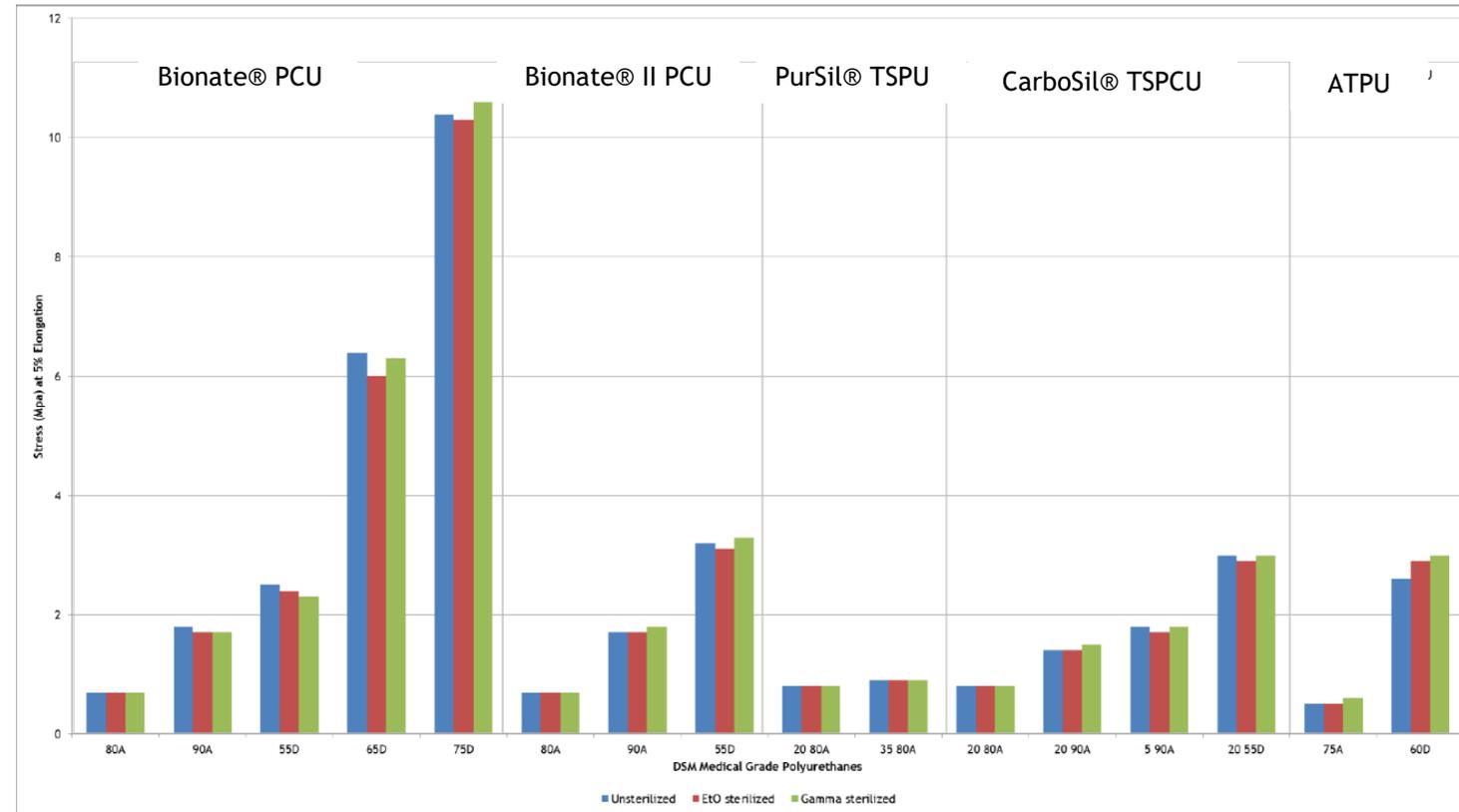


Figure 1. Impact of sterilization method on stress (strength) at 5% elongation

# DSM Biomedical

## *Formulation & Product Development Support*

- **End-to-End support, from feasibility to cGMP manufacturing (via network of partners) supporting clinical and commercial development**
- Dedicated Drug Lab (ISO 13485) for early feasibility & development activities
- Custom development (formulation & polymer) capabilities
- Experienced drug polymer formulation group
- DSM ACT (Analysis, Characterization and Testing) – state-of-the-art analytical capability

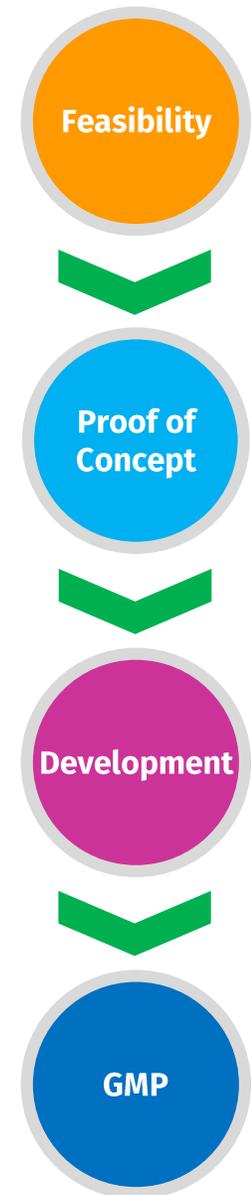
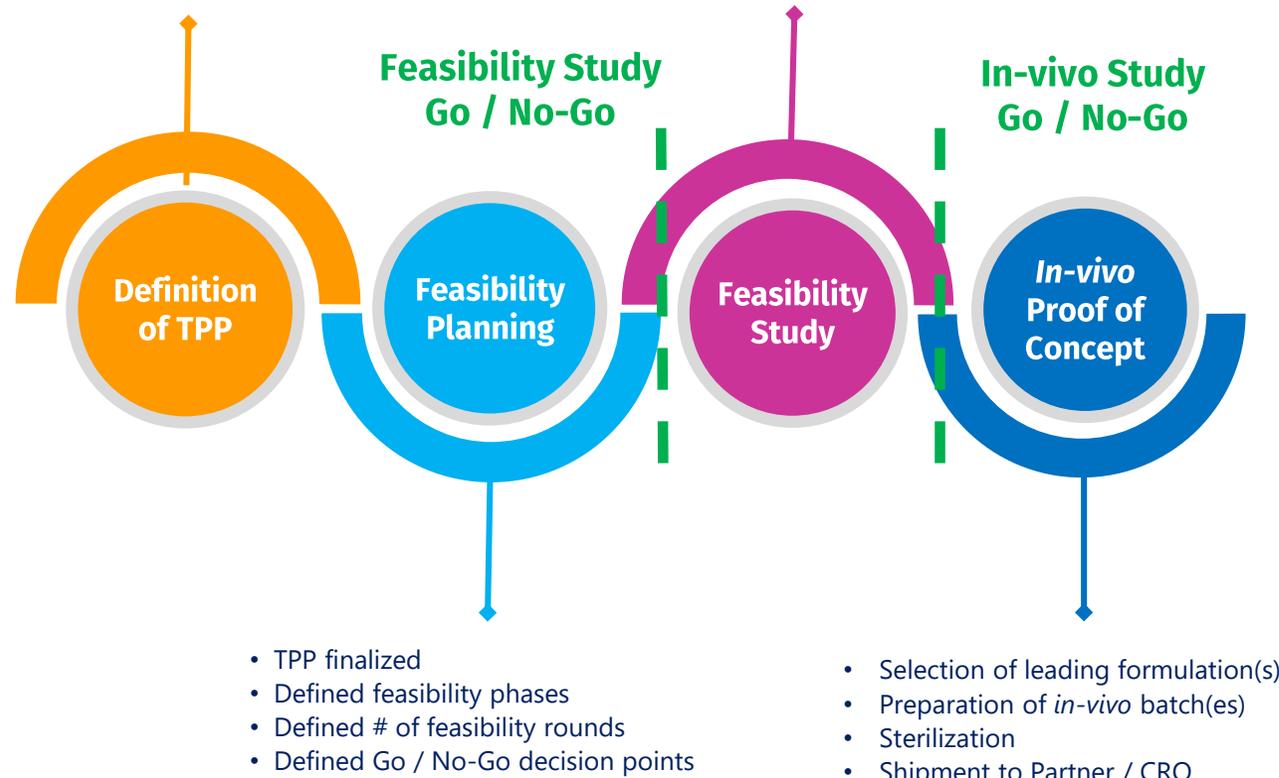


# Feasibility Study Design

## Project Setup Example

- Selection of API and Polymer
- Daily dose / Total load determination
- Desired Duration
- Desired application method
- Selection of form
- Finalized Target Product Profile (TPP)

- API safety assessment
- Analytical method setup – IVR & API load
- Formulation development (# of rounds)
- IVR studies
- Analytical work
- Go / No-Go @ conclusion of each round



# What can we accomplish together?

- We actively work with our partners in Pharma, Biotech and Medical Device Industry on innovative sustained drug delivery applications
- We offer our partners services in development of sustained drug delivery solutions:
  - Access to our state-of-the-art technologies, related expertise and IP
  - Custom formulation development
  - End-to-End support, from feasibility to cGMP manufacturing (via network of partners) supporting clinical and commercial development
  - Out-licensing of in-house programs

# Questions

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