

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

NUTRITION • HEALTH • SUSTAINABLE LIVING




DSM

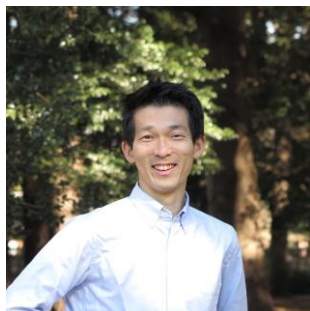
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講演概要

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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DSM at a glance

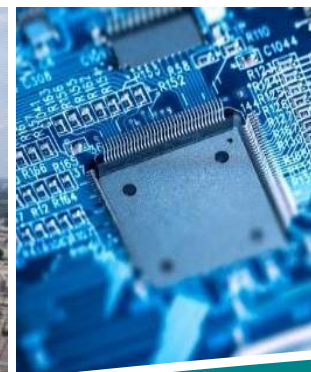
*Purpose-led science to address
the world's challenges in nutrition,
health and sustainable living*

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



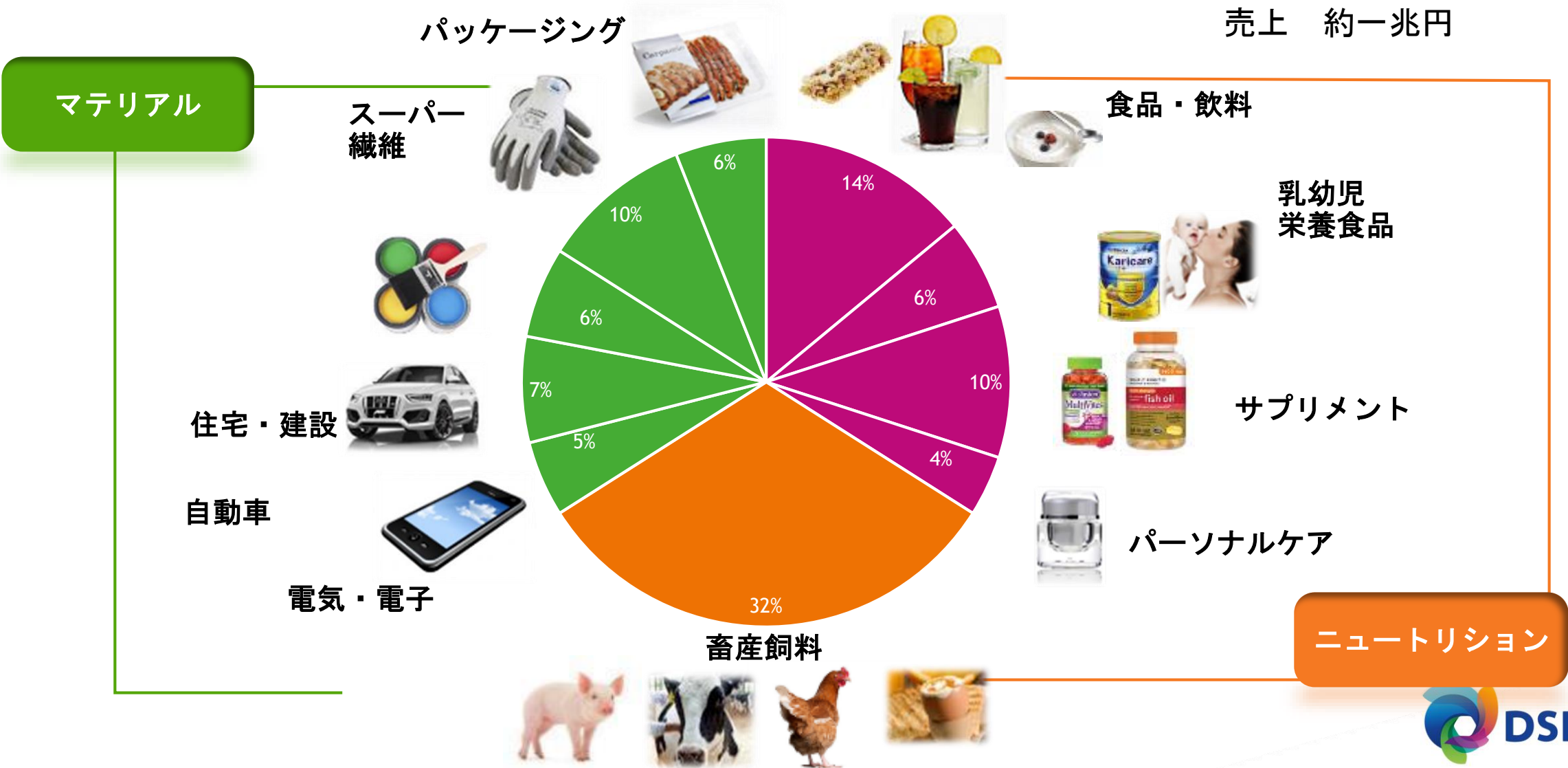
1970~

Unlimited. DSM

2000~



DSMにとっての主要市場

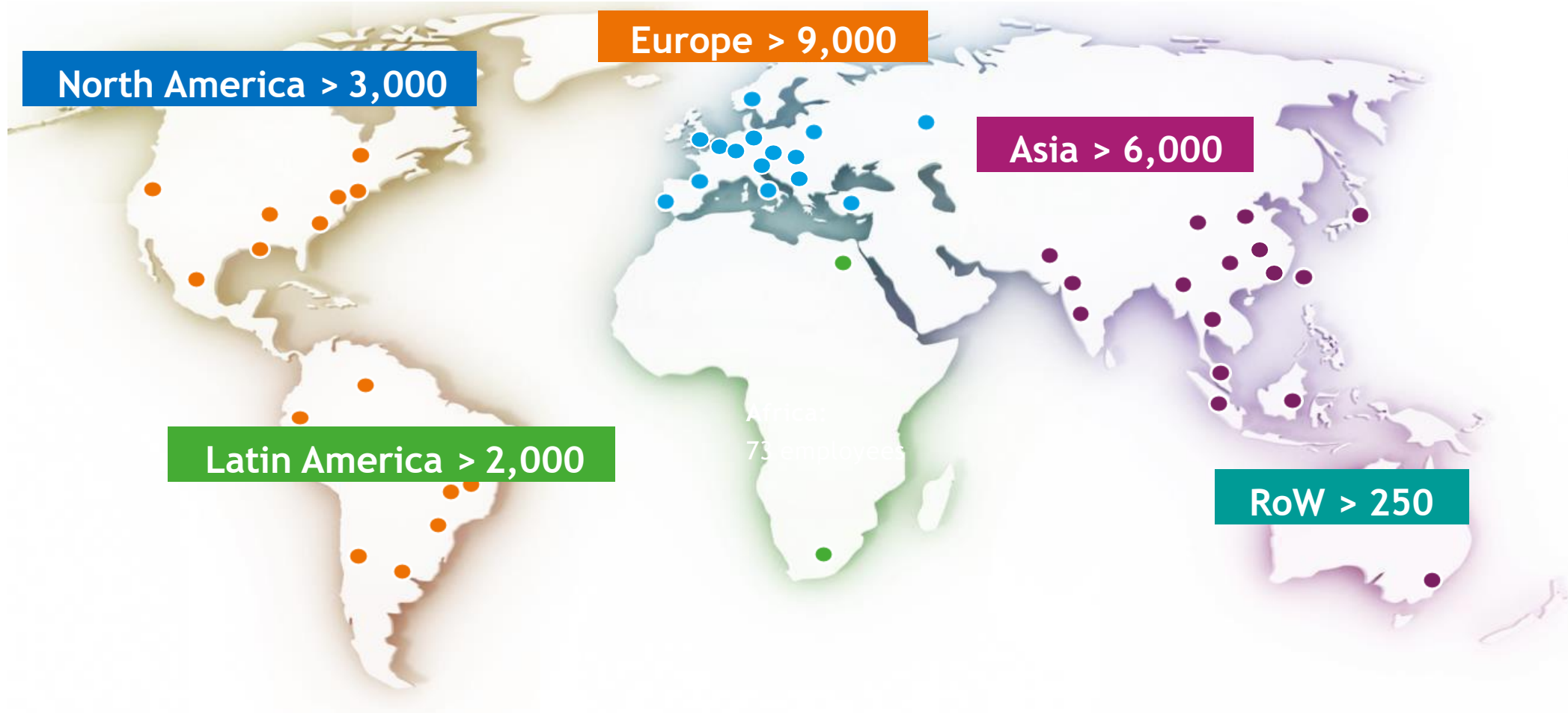


DSMの世界展開

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 その他

「それで、いくらもうかるんだ？」——。持続可能な開発目標（SDGs=エスディージーズ）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



<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



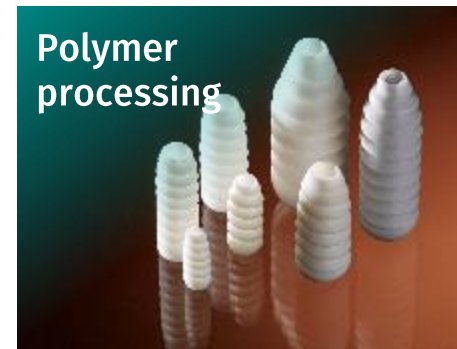
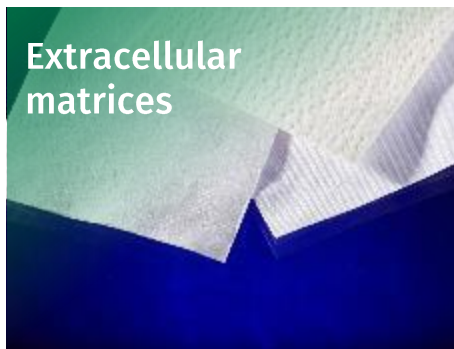
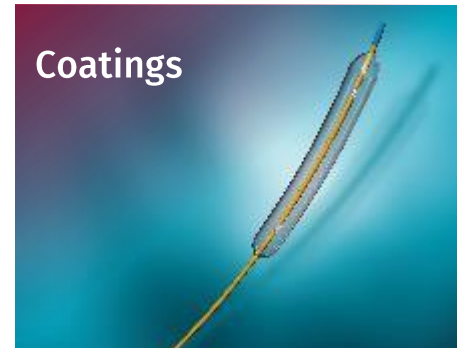
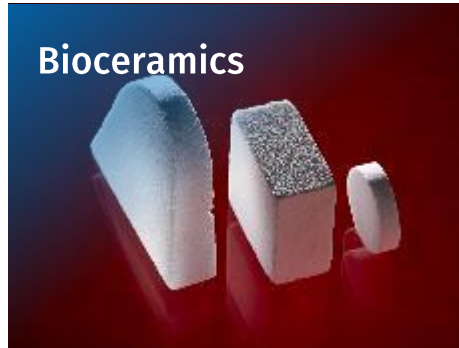
Global presence

~450 employees



Broadest portfolio of biomaterial solutions

Supported by a solid science foundation



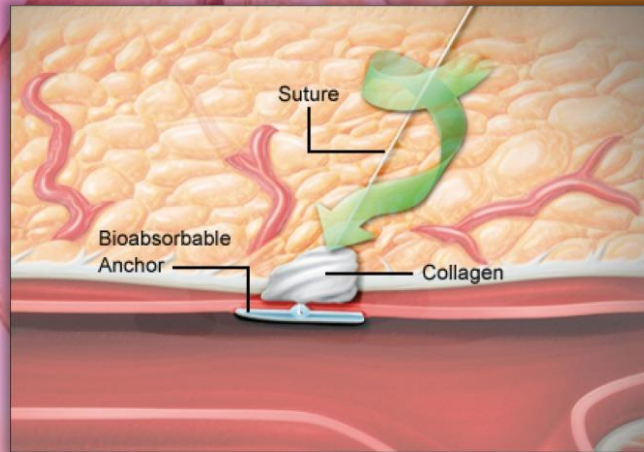
DSM has a solution to assist patients undergoing a catheterization procedure

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

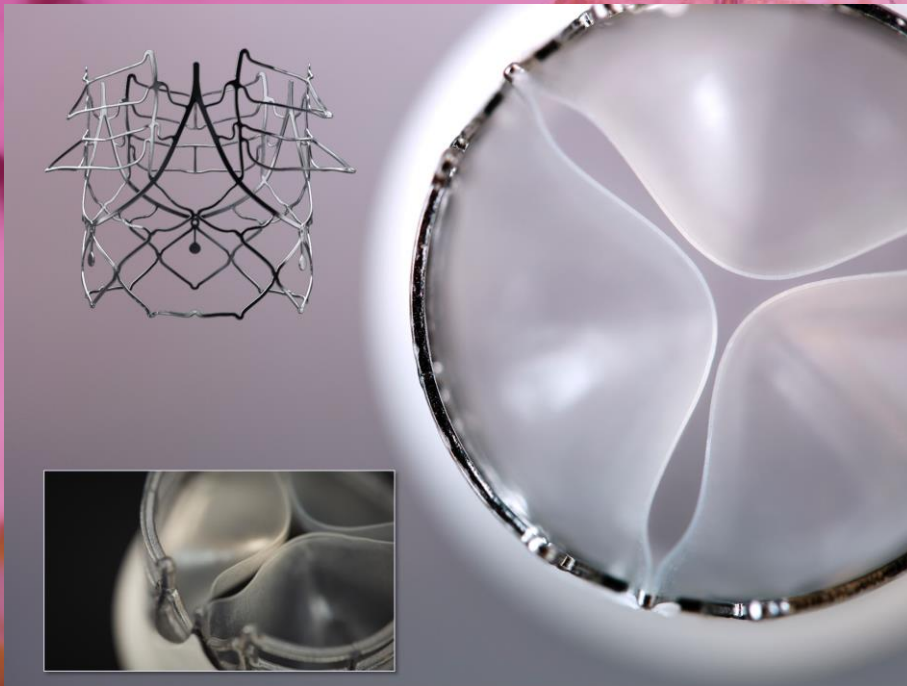
Reduction in
hospital stay
time

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.

3 GOOD HEALTH
AND WELL-BEING



12 RESPONSIBLE
CONSUMPTION
AND PRODUCTION



3 すべての人に
健康と福祉を



12 つくる責任
つかう責任



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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



- Estimated reduced use* of surgical gloves by >40 tons per year
- Over \$3M per year saving in disposables use

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 injectors
 - by 3M per year with 20% market adoption
 - by 12M per year with 100% adoption (US only)



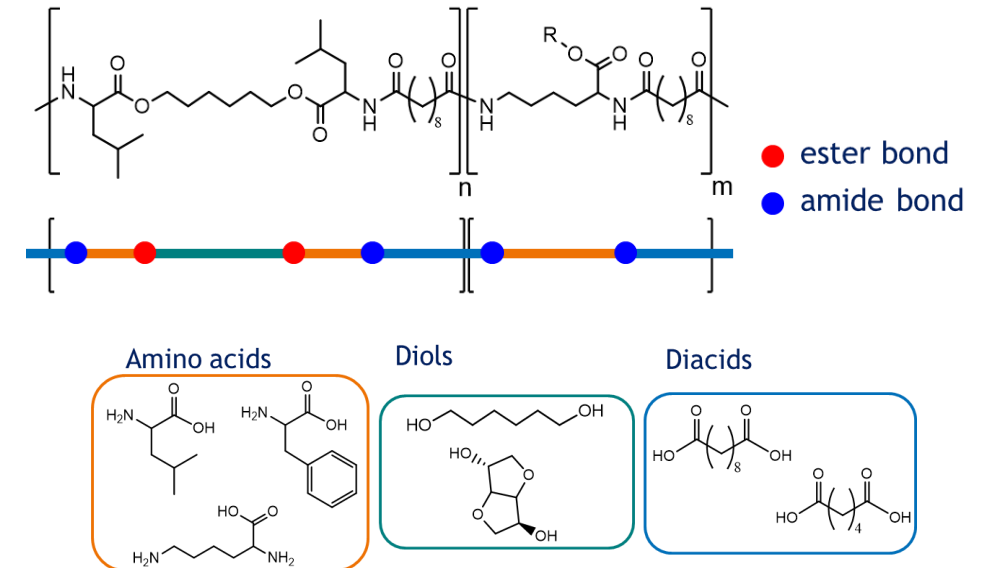
DSM Biomedical Drug Delivery

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

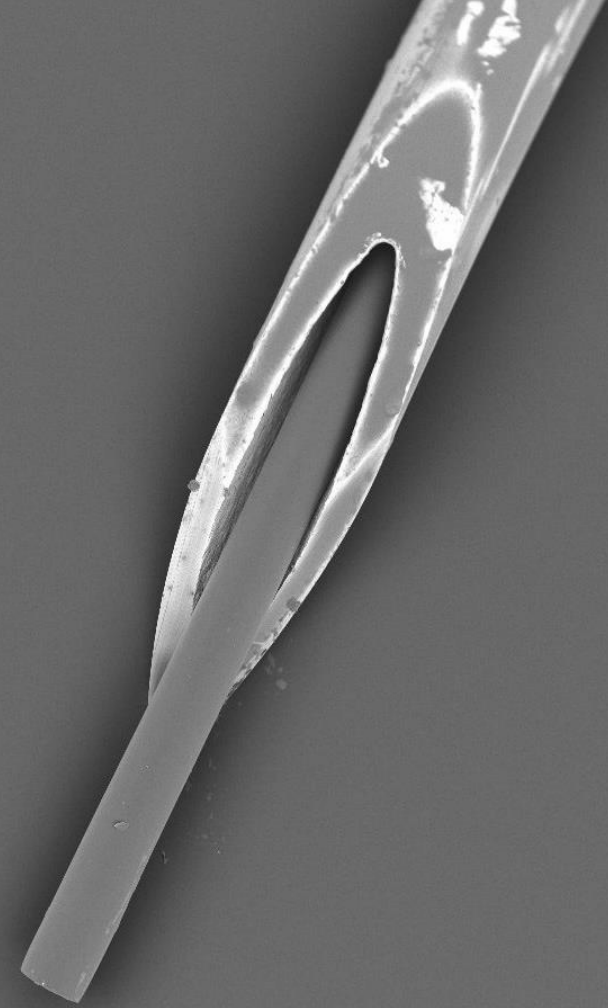
DURHAM, NC & EXTON, Pa.--(BUSINESS WIRE)--Aug. 1, 2018-- Aerie Pharmaceuticals, Inc. (NASDAQ:AERI), an ophthalmic pharmaceutical company focused on the discovery, development and commercialization of first-in-class therapies for the treatment of patients with open-angle glaucoma, retina diseases and 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 200μm – mm
 - API loading 5% – >50% w/w
 - Injectable - 27G (200μm 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

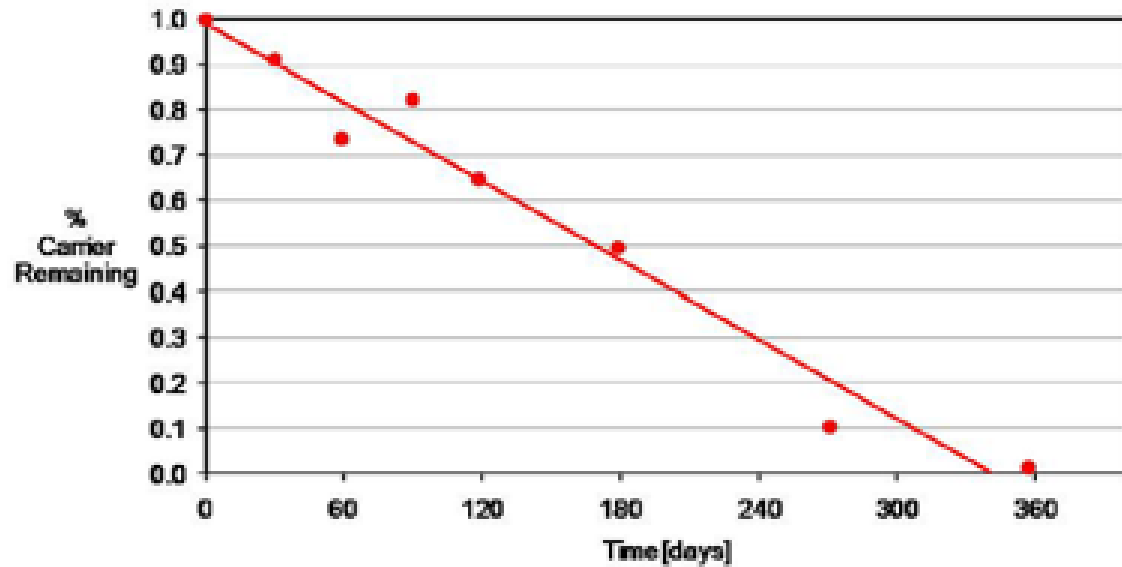
- Typical Specifications:
 - Diameter ~10µm - 100µm
 - Injectable - 30G (10µm MPs) – 23G (10µm MPs)
 - API loading 5%-30% w/w
- Processing Options:
 - Numerous methods available – emulsification, spraying...
- **Long Acting Efficacy proven in pre-clinical studies**
 - Proven superiority of PEA MicroParticle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



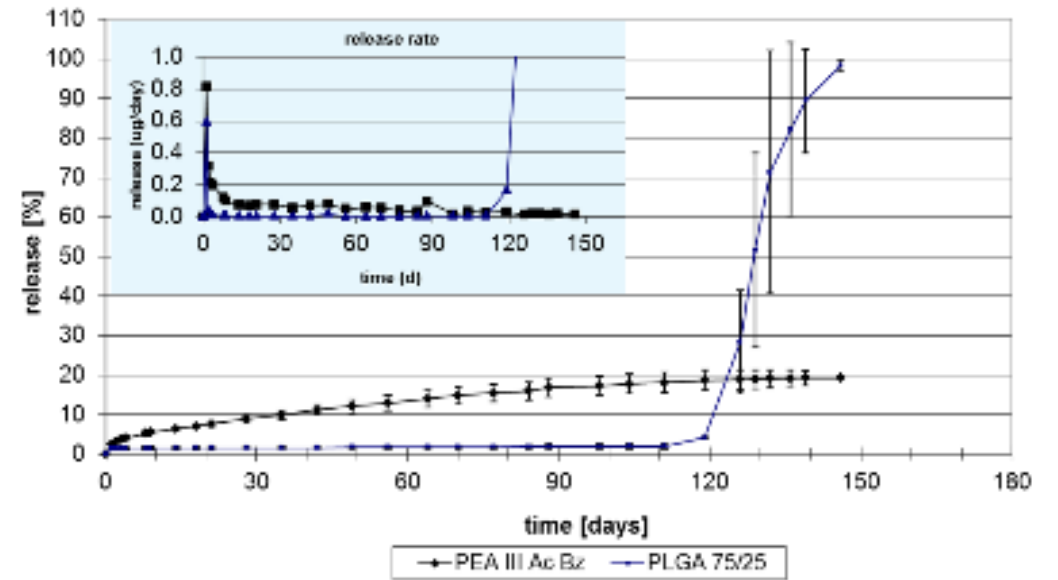
PEA / Form Compatibility

Coatings

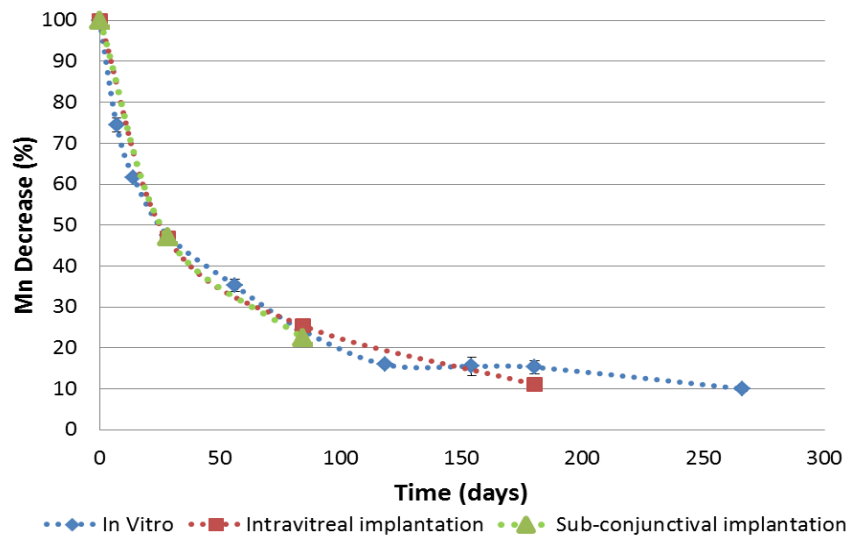
- Compatibility with number of substrates
- Excellent adhesion to metals
- Processing Options
 - Excellent melt processability
 - Solutions processability
 - Unique solubility properties
- **PEA coating in commercial product – Sirolimus eluting coating on Drug Eluting Stent***



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

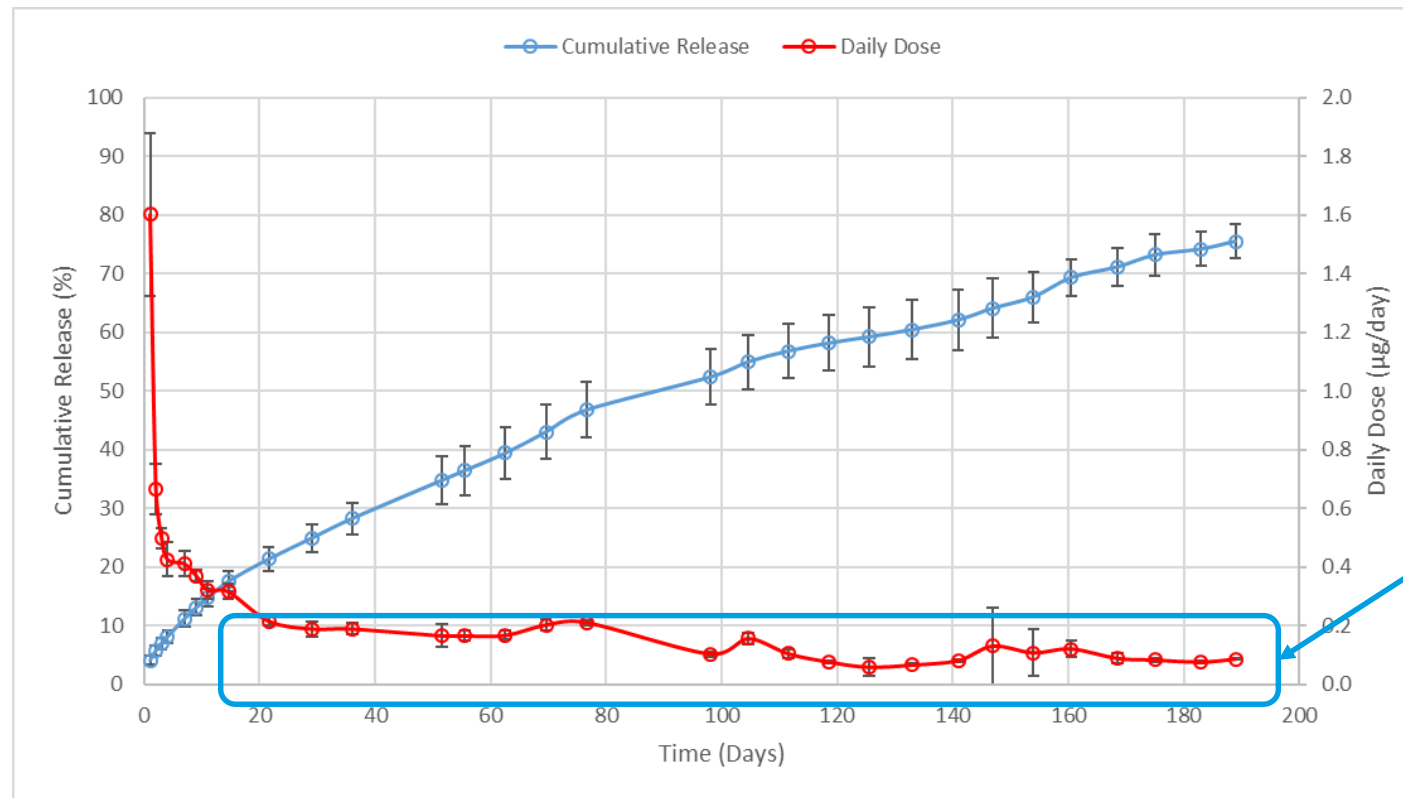


Good correlation in-vitro and in-vivo up to 180 days

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)

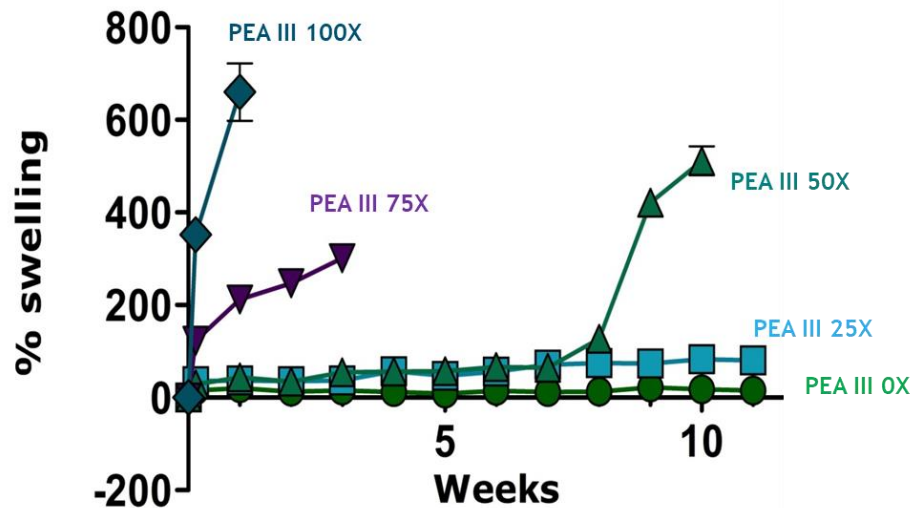
*Formulation / processing of free amine APIs with PolyEsters typically results in disintegration of polymer in 2-7 days

Sustained delivery of biologics

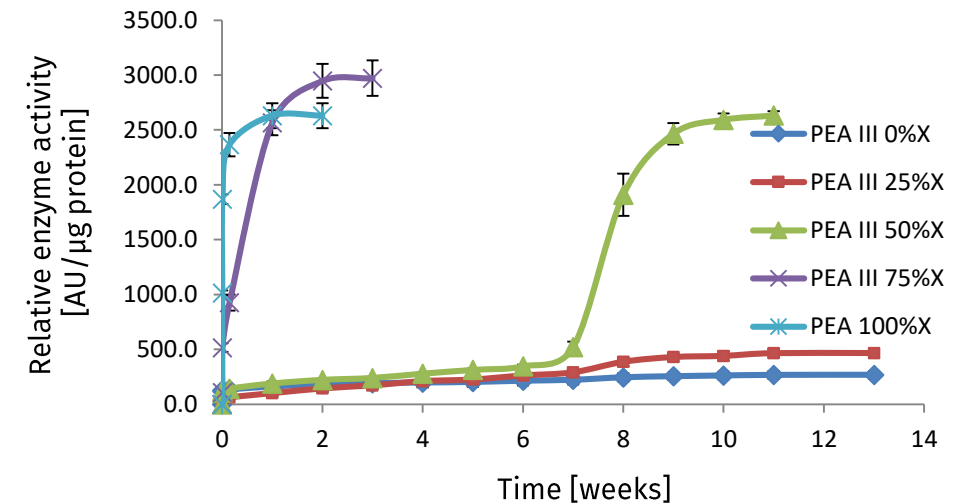
Challenge: Diffusion of large molecules from polymer

Full retention of bioactivity of horseradish peroxidase (44kDa)

Controlled Degradation & Swelling



Release of HRP with Retention of Bioactivity



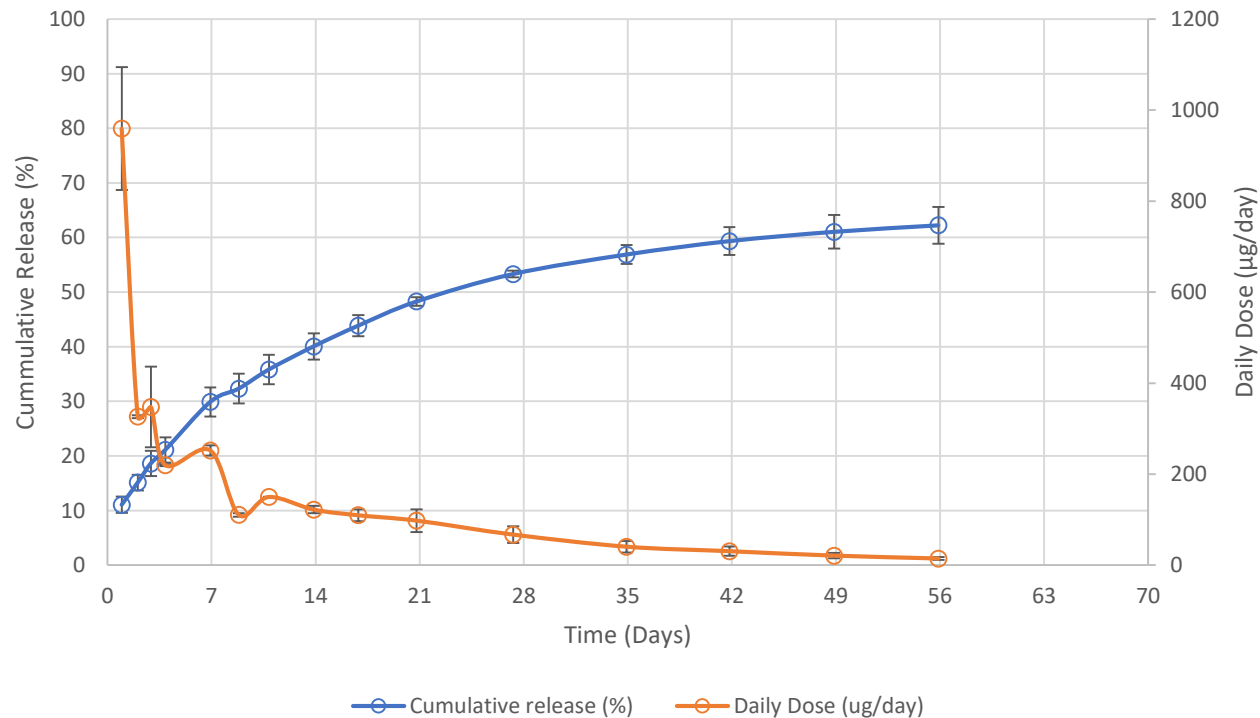
Intrinsic properties of PEA: Lack of degradation-associated acidification of microenvironment contributes to preserving of HRP bioactivity

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

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Proven Biostable polymer platform for sustained drug delivery

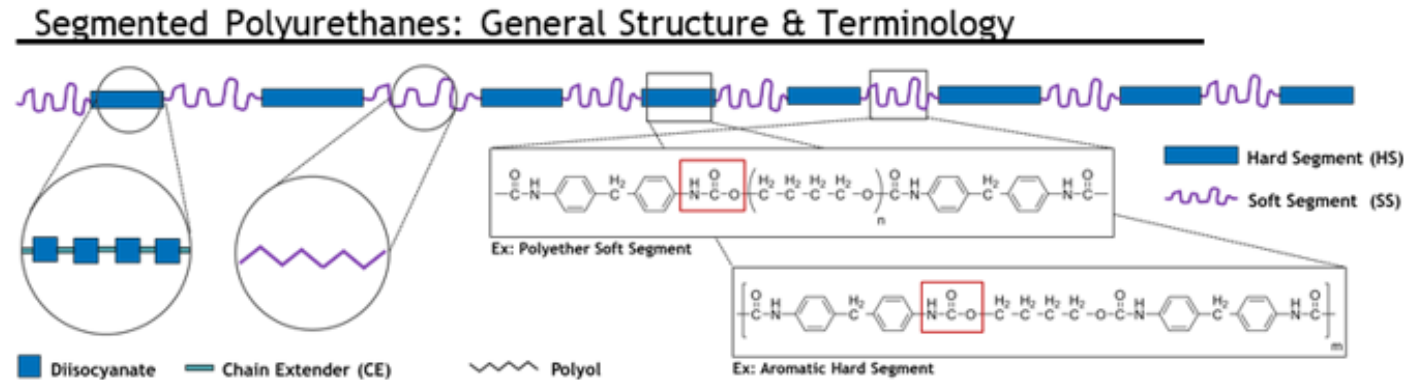
Polyurethane Technology

- ✓ 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

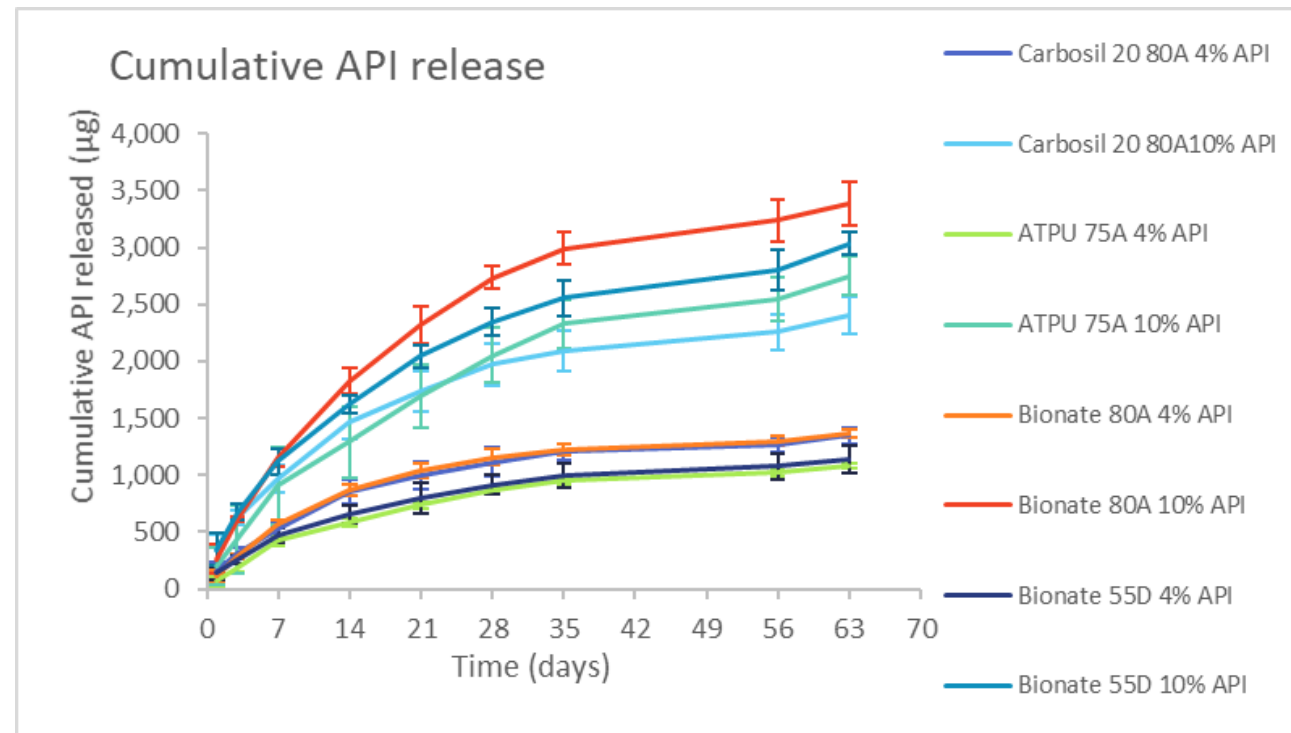
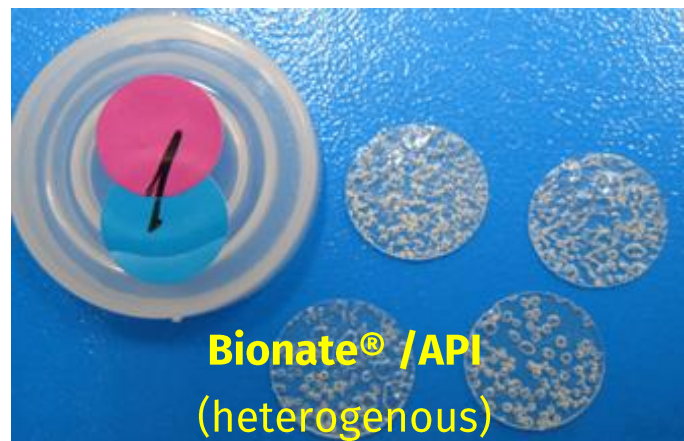
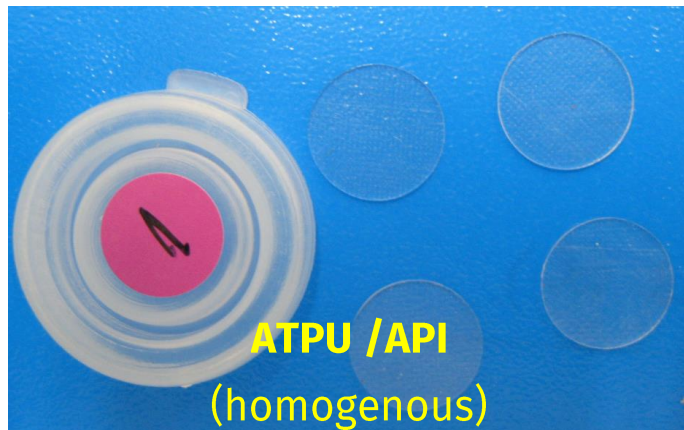


- DSM offers multiple biostable polymers for use in sustained delivery applications
- The diversity in chemical structures of PUs and the possibilities to do functional modifications make them eligible as controllable devices of low molecular weight drugs as well as biotherapeutics.
- A desired profile 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).

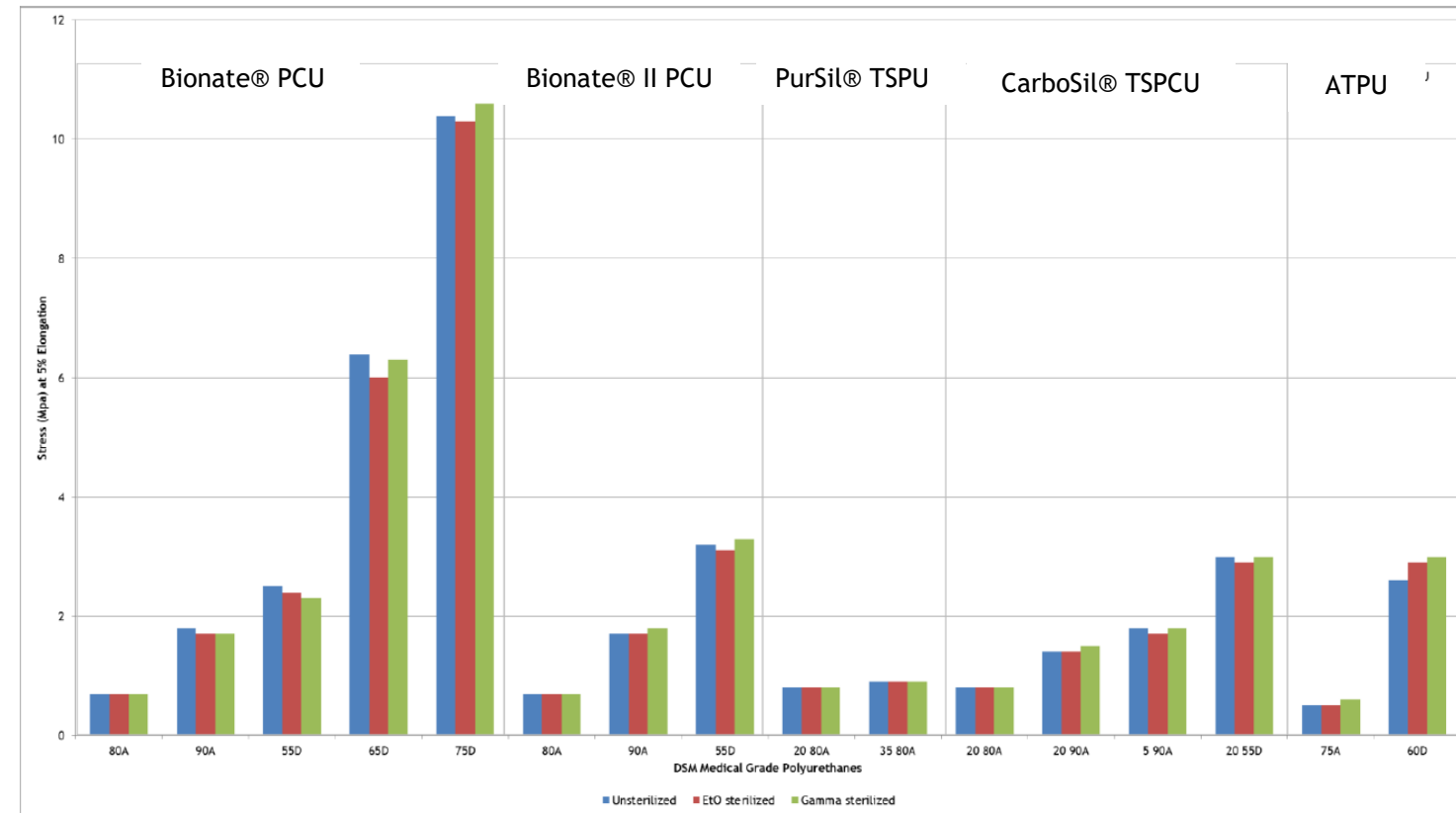


Figure 1. Impact of sterilization method on stress (strength) at 5% elongation

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

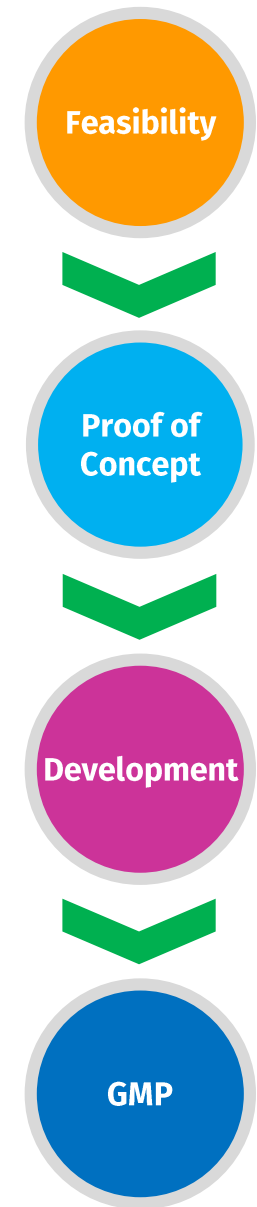
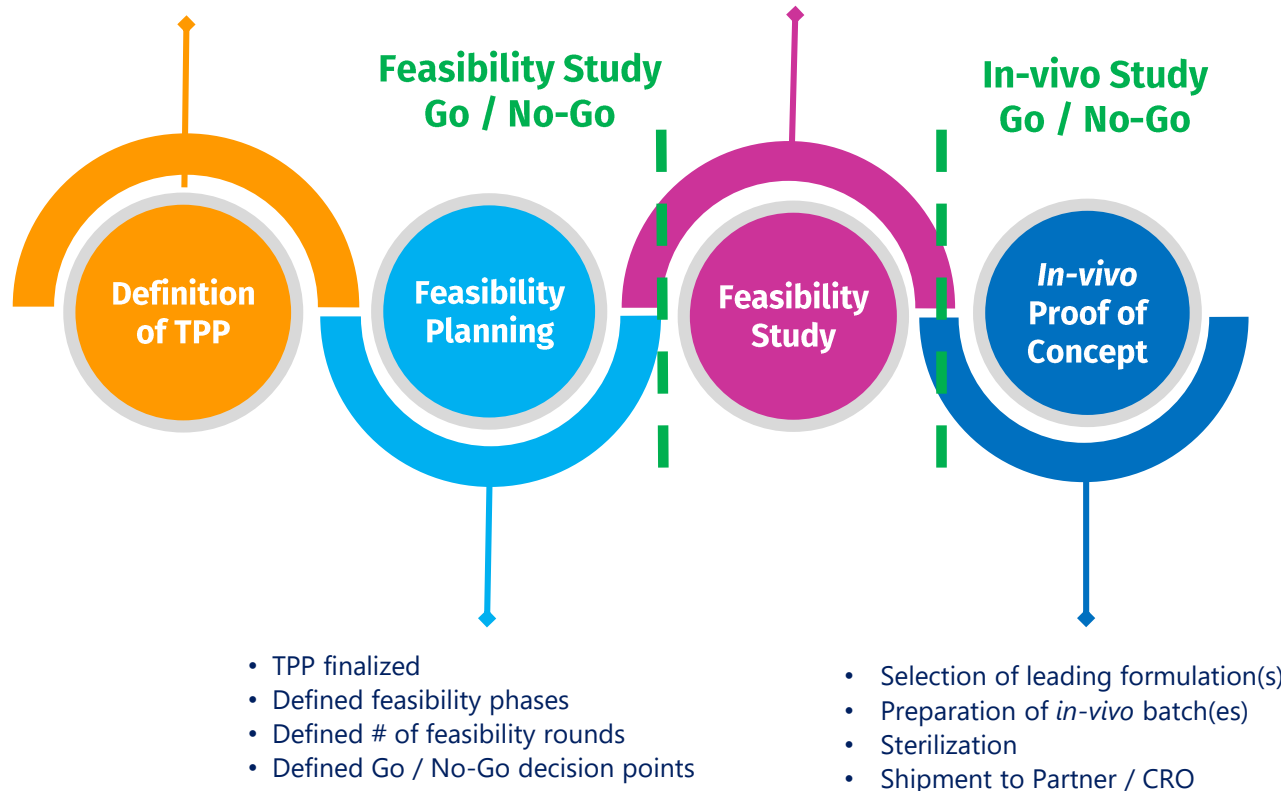


Feasibility Study Design

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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