Overcoming Development Challenges for LAII
Agenda

• Background and Overview of Lubrizol Life Science Health
• Long-Acting Drug Delivery Market Overview
• Trends in LAII
• Our Experience in LAII
• Case Studies
  • Implantable Systems
  • Long-Acting Injectables
• Introducing the Microsphere Feasibility Program
The Health business of LLS serves the medical device and pharmaceutical industries.

The Evolution of Lubrizol Life Science

“The Particle Sciences acquisition further expands Lubrizol’s pharmaceutical development & manufacturing capabilities, providing full service drug product solutions to the market for a variety of dosage forms.”

- Barbara Morgan, Ph.D.
  General Manager
**Pharma Segment Overview**

**Excipients:** inventors and suppliers of polyacrylic acid polymers (Carbopol®, Noveon® AA-1, Pemulen™) and thermoplastic polyurethane (Pathway™)

**Drug Product Development:** contract developers of complex drug products, including insoluble and sterile drug products and drug-eluting systems/devices

**Drug Product Manufacturing:** GMP contract manufacturers of clinical trial and commercial drug products

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*Service offerings along the value chain provides simplification of supply chain*  
*Built for sustainability - A Berkshire Hathaway Company*
CDMO Snapshot

• Founded 1991 as SunSmart (nanoparticle zinc oxide)
• Spun out into a pharmaceutical CDMO (Particle Sciences) in 2004 and acquired by Lubrizol in 2015
• Located in Bethlehem, PA, ~50,000 sq ft integrated facility, 90+ employees
• Full service CDMO including commercial production and traditional CMC services
• Wide range of dosage forms, specialize in complexity
• 7,000+ sq. ft. of GMP production suites: sterile, non-sterile, and high potency
• FDA registered, DEA licensed
CDMO End-to-End Product Services

- Analytic method development and validation
- Pre-formulation & formulation
- Preclinical and clinical trial material production
- Quality/Regulatory CMC support
- Physical characterization
- Stability testing
- Commercial manufacturing
Unique Expertise

• Drug delivery across variety of dosage forms

• Capabilities for complexity
  • Insoluble compounds
  • Drug-eluting devices
  • Long-acting injectables

• Multiple technologies
  • Micro/Nanoparticulates
  • Solid solutions

• Proprietary Modeling Capabilities / QbD Integration

“Innovation requires a thoughtful balance of having the curiosity to investigate with the resilience to solve complicated problems.”

- Robert Lee, Ph.D.
  President
Analytical Core Strengths

- Comprehensive suite of services
  - Method development
  - Physical characterization
  - Forced degradation
  - Commercial validation
  - Long-term stability testing

- Methods - assays, related substances, *in vitro* release, encapsulation efficiency

- Extensive experience with a variety of APIs (small and large molecules) and sample preparation techniques

- Separation (Reverse phase HPLC, SEC, etc.) and detection (diode array, UV-Vis, mass spec, etc.)
ICH Stability

Developmental Studies:

- Homogeneity via Raman
  - Forced degradation
  - MS\textsuperscript{n} structure elucidation
- API / Drug Product
- API / Excipient compatibility via
  - DSC
  - HPLC

Standard ICH & Custom Programs:

- Long-term & accelerated (T/RH controlled chambers)
  - 25 °C/60% RH
  - 30 °C/65% RH
  - 40 °C/75% RH
- Controlled low humidity for semi-permeable conditions
- Photostability
- Stress stability
  - 50 °C/85% RH
- Freeze / Thaw

Over 90 molecules processed in the past 18 months

https://lubrizolcdmo.com/service/ich-stability-testing/
Building on our success in drug development and clinical trial manufacturing, we approach commercial manufacturing with a launch mentality and a first-time-right goal every day.

- Barbara Morgan, Ph.D., General Manager

Commercial Production

**Processing Rooms**
- 6,000 ft² Production / Area Space
- 500 ft² Grade C Flexible Space / Processing Room
- 320 ft² Grade A Filling Room
- Grade A Lyophilizer Loading / Unloading Room

**Utilities**
- WFI
- Clean Steam
- Clean Compressed Air
- Clean Compressed Nitrogen
- Process Waste System

**Foundational Equipment***
- Bausch Model 515 Filler, in-line weight checker (50 vials/minute)
- (RABS) Isolation Technology
- Millrock 120 ft² lyophilizer (capacity: 25,000 10mL vials)

**Dedicated QC Laboratory**
- Analytical Testing
- Purified Water System Testing
- Raw Materials and Component Testing
- Environmental Testing
- TOC Testing

*Client specific dedicated equipment available on demand
[https://lubrizolcdmo.com/service/commercial-manufacturing/](https://lubrizolcdmo.com/service/commercial-manufacturing/)
Long-Acting Drug Delivery: Market Overview
Long-Acting Drug Delivery

**Implantable Systems**
- Vaginal Rings
- Subcutaneous Implants

**Depot Injections**
- Bioresorbable Microspheres
- Bioresorbable Suspensions
- *In situ*-Forming Gels/Implants

**Other**
- LA Oral Dosage Forms
- Combination Products (Medical Devices)

All use a polymer system to provide controlled and/or targeted delivery of drugs.

https://lubrizolcdmo.com/therapeutic-area/long-acting-drug-delivery/
# Long-Acting Drug Delivery

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Implant</th>
<th>Injection</th>
<th>Oral</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing Frequency</strong></td>
<td></td>
<td>Once every 30+ days</td>
<td>Once every 7+ days</td>
<td>Various</td>
</tr>
<tr>
<td><strong>Enabling Technologies</strong></td>
<td>HME IM Cryo-milling</td>
<td>Microspheres Bioabsorbable polymers Homogenization Microfluidization Lyophilization</td>
<td>HME IM Cryo-milling</td>
<td>Various</td>
</tr>
<tr>
<td><strong>Example(s)</strong></td>
<td>Vaginal ring Subcutaneous implant</td>
<td>Bioresorbable microspheres Bioresorbable suspension</td>
<td>Gastro-retentive pill</td>
<td>Steroid-eluting pacemaker leads</td>
</tr>
</tbody>
</table>

Our LA Experience – Past 5 Years

25+ Implantable Systems

12+ Depot Injections

10+ Drug-Eluting Med. Devices
What We’ve Seen in LAII

01

Growth in R&D Funding

• Increased grant funding, partnerships to drive:
  • Improved patient compliance
  • Drug delivery in low/middle income countries

02

Growth in 505(b)(2) Utilization

• Use of novel formulation technologies and excipients
• Interest in lifecycle management
• Need for CDMOs with flexibility in formulation approach and excipient selection

03

Increased Clarity on Complex Generic ANDAs

• FDA programs driving renewed interest in long-acting injectables
• Improved guidance is lowering barrier for applicants
• Supplier of highly customizable Pathway™ TPU Excipients

• Relationship with Corbion for bioabsorbable polymers (e.g., PLGA)

• Number of projects with silicone, EVA, PCL, client-provided proprietary polymers, etc...

More shots at goal increases your chances of success!

• Implants: hot melt extrusion, coextrusion, injection molding, cryomilling, high-shear mixing

• Depot Injections: sterile liquid and powder filling, lyophilization, homogenization, microfluidization, TFF

• Solubility Enhancement: nanomilling, spray drying, LyoCells®

https://www.corbion.com/biomedical/products/polymers-for-drug-delivery
Implantable System Case Studies

Vaginal Rings

Subcutaneous Implants
Implantable Systems

Non-infringing generic NuvaRing
  • EMA generic
  • Details: Develop a ring with modified design and/or excipients to enable approval in Europe (similar to 505(b)(2))
  • Our Role: Full development, including scale-up and tech transfer back to client for commercial production

Biodegradable implant for subcutaneous delivery of NCE
  • NDA
  • Details: Tech transfer of proprietary process for GMP manufacturing to support phase IIa clinical trial
  • Our Role: Tech transfer and manufacturing

https://lubrizolcdmo.com/dosage-forms/implantable-devices/
Delivery of Multiple APIs from a Pathway™ TPU Reservoir System

- **Objective:** Enable the delivery of two APIs with different partition coefficients and solubility
- **Purpose:** Contraception / HIV Prevention
- **Dosage Form:** Vaginal Ring
- **Design:** Reservoir
- **APIs:** Tenofovir (TFV) and Levonorgestrel (LNG)
- **Polymers:** Pathway™ Hydrophobic and Pathway Hydrophilic™
- **Duration:** 90+ days *in vitro*

LLS Health supplied the polymer and performed Phase I clinical trial manufacturing. Currently being scaled for Phase II clinical trials.


https://www.lubrizol.com/Life-Sciences/Products/Pathway-TPU-Excipients
Long-Acting Injectable Case Studies

- Bioresorbable Suspensions
- Bioresorbable Microspheres
- In situ-Forming Gels/Implants
Bioresorbable Suspensions

Subcutaneous bioresorbable gel depot
- 505(b)(2)
- Details: Biologic with injectable polymeric system
- Our Role: Formulation optimization, scale-up, GLP and GMP manufacturing, eventually commercial production
- Status: scaling and taking client into GLP toxicology study

Intramuscular microparticle
- ANDA
- Details: Intramuscular depot formulation with complicated IP landscape
- Our Role: Design through BE and commercial production via aseptic nanomilling
- Status: In discussions with potential client for commercial manufacturing

https://lubrizolcdmo.com/dosage-forms/microparticle-depots/
Microsphere Depot Injections

**Biodegradable microsphere w/ surface modification for intravitreal injection**
- NDA, ROA: Ophthalmic
- Details: Production, modification, and fill/finish of lyophilized microparticle
- Our Role: Tech transfer, clinical production of 8x200 g batches, commercial scaling to 2 kg powder batch
- Status: currently in Ph II clinical trial

**Biodegradable microsphere containing octreotide for generic Sandostatin LAR® Depot filing**
- ANDA, ROA: Intramuscular
- Details: RLD requires a large volume of flammable solvent and a specially-designed facility to manufacture
- Our Role: Designed a proprietary manufacturing process that bypasses large volume of flammable solvent
- Status: developed and in negotiations with potential partners for commercialization

https://lubrizolcdmo.com/dosage-forms/microparticle-depots/
Microsphere Feasibility Program
*For long acting injectables*

**12 weeks**

**Select Polymers for Screening**
Develop a target product profile and design a screening study using best-in-class PURASORB® polymers.

**Manufacture Microspheres**
Generate small batches of microspheres containing your API for characterization.

**Characterize Microspheres**
Identify promising formulation(s) and determine a route forward for optimization and scale-up.

LLS Health is a leading solutions provider for long-acting injectables, and we are prepared to take your project into scale-up and GMP manufacturing.

LLS Health: The Preferred CDMO for Complex Drug Products

Drug delivery across a variety of dosage forms

Capabilities for complexity

Polymer and technology agnostic

From concept to commercialization, we deliver!

https://lubrizolcdmo.com/
Thank You!

Learn more at www.LubrizolCDMO.com