DRUG DELIVERY EXPERTS

CHANGING LIVES THROUGH DELIVERY TECHNOLOGY

www.ddelabs.com
Peptide Formulation and Delivery Technology

Current State and Future Directions

Chinese Peptide Company Scientific Symposium
17 October 2019

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President Boulder Peptide Society
President and CEO Drug Delivery Experts, LLC
More than 60 approved peptide products (8 withdrawn) 155 are in active clinical development

- Large majority of these products are immediate release
- Most are presented as drug product in vial and syringe, pen, pre-filled syringe, and auto-injector systems
- Aqueous solution formulations are most common in US/EU
- China and Japan have more lyophilized products

• Peptide delivery products have been on the market many years
  • Peptides in long-acting injectable and implantable systems
  • Peptides in nasal formulations
  • Peptides in pulmonary inhalation systems
Peptides in long-acting injectable and implantable systems
  - Microspheres, gel forming polymers, lipid gel formers, implantable rods (non-degradable and biodegradable)
  - Viadur titanium rod (2001 - withdrawal 2007) - 12 month LHRH
  - Intarcia just resubmitted ITCA 650 – exenatide 6 month implant
Reliable way to achieve 1 to 6 month delivery of potent drug
  - Formulation approaches / product profiles well understood
  - Reasonable exposure consistency can be achieved
Challenges
  - Initial release can be a problem to overcome
  - Interactions with formulation (conjugation) sometimes an issue
### APPROVED PEPTIDE PRODUCTS IN LONG-ACTING FORMULATIONS / DEVICES

**36 Approved Long-Acting Products Based on Polymer** – 12 of them are peptides

**37 Approved Long-Acting Oil Suspensions** – 3 of them are peptides

<table>
<thead>
<tr>
<th>#</th>
<th>Product</th>
<th>Drug</th>
<th>Company</th>
<th>Technology</th>
<th>Indication</th>
<th>Route</th>
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<tbody>
<tr>
<td>1</td>
<td>Adalimumab</td>
<td>infliximab</td>
<td>Denali Therapeutics</td>
<td>Biopolymer</td>
<td>Periodontitis</td>
<td>Oral/periodontal</td>
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<td>2</td>
<td>Bydureon</td>
<td>exenatide</td>
<td>AstraZeneca</td>
<td>Microsphere</td>
<td>Diabetes, type II</td>
<td>SC</td>
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<td>3</td>
<td>Eliquis</td>
<td>lepirudin</td>
<td>Pfizer</td>
<td>Artgeli</td>
<td>Prostate cancer</td>
<td>SC</td>
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<td>Lupron Depot</td>
<td>leuprolide acetate</td>
<td>Abbvie</td>
<td>Microsphere</td>
<td>Prostate cancer, central precocious puberty</td>
<td>IM</td>
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<tr>
<td>5</td>
<td>Nutropin Depot (discount)</td>
<td>Human growth hormone</td>
<td>ALKS / DNA</td>
<td>Microsphere</td>
<td>Growth stature</td>
<td>SC</td>
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<td>Oxydex</td>
<td>dexamethasone</td>
<td>Allergan</td>
<td>Implant (rod)</td>
<td>Retinal vein occlus, uveitis, diab mac edema</td>
<td>Intravitreal</td>
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<td>PROPEL and SINJUVA</td>
<td>mesepramone furoate</td>
<td>Procept Pharma</td>
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<td>pasireotide malonate</td>
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<td>buproprion</td>
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<td>goserelin acetate</td>
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</table>
• Peptides in nasal formulations
  • Solution based nasal spray devices commercially available
  • Proprietary systems for targeting regions of nasal cavity
• Works well with permeation enhancers and small peptides
• Some data suggesting nose to brain enhancement
• Challenges
  • Variability in exposure is high (50 to 100% CV)
  • No way to slow formulations for short-acting peptides due to nasal muco-ciliary clearance (10 to 20 minutes)
  • sCT, DDAVP, buserelin, oxytocin, glucagon (2019 approval)
• Peptides in pulmonary inhalation systems
  • None approved except for Insulin (a large peptide)
  • Approved two times
    • Exubera (Pfizer – Nektar) 2006, withdrawn 2007
    • Afrezza (Mannkind) 2014 (permeation enhancing)
• No permeation enhancer required for absorption
• Biologics well absorbed across lung epithelium (40%) 
• Bioavailability typically 5 to 7% overall
• Reliable way to achieve SC like variability in exposure
• Challenges
  • Potential for hormone lung effects
  • Not a good approach for a titrated product

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• Development of maturing non-injectable delivery systems
  • Microneedle programs in phase 2 and 3
    • Parathyroid hormone (Radius)
  • Peptides in oral formulations for topical delivery
    • Linaclotide, Palatin program (John Dodd)
  • Peptides in oral delivery devices
    • Microneedle systems – Rani SmartPill, MIT/NOVO SOMA
    • Liquid injection - Progenity, Propel Biologics JetCAP
  • Peptide systems for blood brain barrier transport
    • Feldan Shuttle, TAT and CPP peptides
MATURING DEVICE TECHNOLOGIES

Microneedle Intradermal Injection

- Coated microneedle
- Dissolving solid microneedle
- Hollow microneedle
- Bioavailability >50% vs SC
- No regulatory precedent
- Many programs in late development

Devices for Oral Delivery
Rani Therapeutics Smart Pill

- Solid microneedle in enteric capsule
- Bioavailability >50% vs SC
- Microneedle actuation in GI is novel
- No regulatory precedent
- Rani Phase 1 completed
- Rani Phase 2 octreotide (ongoing)

MIT/NOVO SOMA System

Propel Biologics JetCAP

Progenity

GI Diagnostics And Delivery

www.ranitherapeutics.com
SUMMARY OF PEPTIDE DELIVERY SYSTEMS

Decision to move beyond a vial and syringe has practical implications. Choices come with higher reward, but, higher development cost and risk.

Injection Systems
- New Polymer
- New Scaffolds
- Lipid systems
- PEG, Acyl, Alb, Fc conjugates
- Microspheres, Gels, Pumps, Suspensions
- Pen Injectors
- Vial Syringe

Product Characteristics
- Moderate to High BA
- Acceptable Variability
- Continuous Exposure

Non-Injection
- Oral Device
  - Low Dose
  - High BA
  - Variability
- Oral Form
  - Pseudogludate
- Microneedle
  - PTH in phase 3

Product Characteristics
- Low Dose
- Low BA
- Variability
- Pulsatile Exposure

Risk
- Reward

Vial = Commercialized Products
- Syringe = Products in Development

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THANK YOU TO CPC TEAM AND AUDIENCE

GREETINGS FROM SAN DIEGO
WE THRIVE ON SOLVING YOUR MOST CHALLENGING PROBLEMS