Peptide Product Development Considerations

• What Makes a Product Development Scientist?
• Introduction and Delivery System Preferences
• The Importance of Target Product Profile
• Exenatide Life Cycle Program
• Questions
How Did I Get Here? Lots of Help!

Mentors and Influences and Experiences

1981
YE Rhodes - DI Schuster - CS Foote - JI Berson --- SS Steiner - WC Vincek - A Baron -- D Bradbury -- Friends and Colleagues

Physical Organic Chemistry
Photochemical and Thermal Rearrangements
Singlet Oxygen and Electron Transfer Rxns

1992
Small, Mid-size Biotech, Drug Delivery
Lab and team startups
Functional leader and team leader

Startups and Consulting
CTO, Head R&D
Drug Delivery Experts

2011

2014

Small,
Mid-size
Biotech,
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1981
1992
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NYU
NYU
UCLA BRUINS

MannKind Corporation.

SKSOCULAR

ADVANCE THERAPEUTICS

DiaVacs

GUILFORD PHARMACEUTICALS

AMYLIN

Sensulin
Center of Excellence for Peptide Drug Product

**Vision**
Changing Lives Through Leadership in Drug Delivery Systems

**Mission**
Bringing Our Global Partners the Best Drug Product Solutions

Specialists in combination drug product development
Complex formulation design and device integration
Deep experience in peptide drug development
30 highly experienced PhD and BS scientists
Achieving Target Product Profile Requires A Deep Understanding of Active, Formulation, Device

Leveraging a deep understanding of molecular properties, formulation, and device
Integrating delivery system R&D project into your development program
Optimizing target product profile to enhance value proposition

Discovery Support
- Lead molecule profiling
- Clinical candidate evaluation
- Biologic half-life extension

Drug Product Development
- Formulation design
- Drug product development
- Analytical methods

Device Development
- Device identification
- Integration with formulation
- Development and selection
Market Preference for Non-invasive Delivery

Injection

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Oral

device --- Transdermal --- patch

Nasal
Buccal
Sublingual

Once per day >>> BID or TID
Injection Frequency Preferences

Product Profile Parameters
- Complexity of product handling
- Ready-to-use product
- Needle size for injection (viscosity)
- Injection force (viscosity)
- Pain on injection (volume)
- Duration of injection (volume)
- In-Use stability constraints

Decreasing Injection / Administration Frequency

Multiple Daily Inj
Daily Injection
Weekly Injection
Monthly Injection
Quarterly Injection
6 to 12 Month Inj

Patient Self-Injection Common: Product Profile More Critical

Potential for Office Administered Product: Good Product Profile Not Critical
Limited Examples of Commercially Tested Systemic Delivery Systems for Peptides

**Injection Systems**

- New Polymer
- Scaffolds
- Lipid systems
- PEGylation
- Microspheres with Reconstitution
- Pen Injectors
- Vial and Syringe

**Characteristics:**
- Moderate to High BA
- Acceptable Variability
- Continuous Exposure

**Non-Invasive**

- **Pulmonary**
  - Pulmozyme, Insulin
- **Oral**
- **Transdermal**
- **Nasal**
  - DDAVP, sCT, Buserelin, Nafarelin, Oxytocin

**Characteristics:**
- Low Dose
- Low BA
- Variability
- Pulsatile Exposure

**Risk vs. Reward**

- Commercialized Products
- Products in Development
### Importance of Target Product Profile
Most Parameters Affect the User Experience

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Suggested for Consideration</th>
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<tbody>
<tr>
<td>Route of Administration</td>
<td>Subcutaneous, Intravenous, Intramuscular Non-invasive (Nasal, microneedle)</td>
</tr>
<tr>
<td>Dose Frequency and Pharmacokinetics</td>
<td>Daily or multiple daily injection (with native PK profile) Weekly, Monthly, Quarterly (with continuous exposure)</td>
</tr>
<tr>
<td>Projected Dose</td>
<td>Projected human, animal, toxicity doses (drives concentration in dosage form)</td>
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<tr>
<td>Dose Volume</td>
<td>&lt; 1mL for subcutaneous injection (also drives concentration in dosage form)</td>
</tr>
<tr>
<td>Ease of Use and Handling</td>
<td>Easily injected through a 26G or smaller needle Minimal handling by care giver (simple reconstitution)</td>
</tr>
<tr>
<td>Device and Container Closure System</td>
<td>Vial and syringe, pre-filled syringe, dual-chamber syringe, cartridge Multi-use pen, or auto-injector</td>
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<tr>
<td>Stability In-use</td>
<td>25°C, 1 week to 1 month</td>
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<tr>
<td>Stability for Long Term Storage</td>
<td>2-8°C, minimum 24 months</td>
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Sustained Release Formulation Approaches

- Atrigel
- Liposome
- In Situ Gel-Forming System
- Microsphere
- Non-Aqueous Solution/Suspension
- Implant

Increasing Drug Potency

- Daily Injection
- Weekly Injection
- Monthly Injection
- Quarterly Injection
Highly potent drug – 10 to 20 micrograms per day
Highly water soluble peptides – 100s mg/ml
Good stability in aqueous solution
Good metabolic stability
Half-life of 1 to 2 hours in humans
Choices for delivery system are virtually unlimited
Yet, mistakes can be (and were) made
Drug Product Profile Example: Exenatide

Byetta (exenatide injection)
- Launched by Amylin and Eli Lilly Partnership (now owned by Astra Zeneca)
- Discovered by John Eng (VA Hospital) 1996

Exenatide Drug Substance
- 39 amino acid peptide

Container Closure System
- 1.2 & 2.4 mL cartridge for pen
- 0.25 mg/mL strength

Disposable Pen-injector
- 5 mcg or 10 mcg per injection
- Storage : 2 year shelf-life
- In-use: 30 day period at RT
GLP-1s Move to Maximize Continuous Exposure

Byetta (exenatide)
Half-life 1-2 hrs

Liraglutide (Victoza)
Half-life 13 hrs

Bydureon (exenatide MS)


US 2005 EU 2006

0.9%

-0.9%

EU 2009 US 2010

EU 2009
US 2010

HbA1C Reduction
-1.5%

US 2010 EU 2011

US 2012

Kim D et al. Dia Care 2007;30:1487-1493

(index for each dose)
Microspheres to Achieve Continuous Exenatide

Exenatide Weekly PLGA Microspheres (SEM)

License PLGA Technology from Alkermes (2000) (Neutropin Depot) was precedent for work
Exenatide Microsphere Manufacture and QC

Exenatide MS Release and Polymer Degradation

A. Cumulative Release vs Time (days)
B. Molecular Weight vs Time (weeks)

Exenatide MS Particle Size Distribution

A. Particle Size Distribution
B. SEM Images

Polymer Type, Formulation and Process Controls Release Profile and Pharmacokinetics

Particle Size is Controlled by Process and Dictates Device and Needle Guage
Exenatide Microsphere (Bydureon) Life Cycle

- Bydureon is an exenatide microsphere formulation
- Vial and syringe, pen, suspension in auto-injector
- MS injectable suspension to be submitted by AZ 20172018?

Bydureon (EU 2011 US 2012)
Once weekly SC injection
2 mg per week dose

Bydureon Pen (US 2014)
Once weekly SC injection
2 mg per week dose

Bydureon Suspension (US 2018?)
Once weekly SC MS suspension
2 mg per week dose

Vial and syringe presentation discontinued Jan 2016 with pen launch
Bydureon: Single Dose PK Profile (10 to 12 weeks)

**SD PK Dose Selection Study 2.5 mg, 6 mg, 7 mg, 10 mg**

- Initial release in first day subject of significant formulation and clinical work
- Target product profile was once per month injection – could not be achieved due to initial release
- 300 pg/ml was achievable with low initial release by weekly injection of the same formulation
Exenatide Delivery Opportunities Evaluated

- Nasal formulation taken into clinic
- Transdermal microporation taken into clinic
- Pulmonary dry powder evaluated in preclinical work
- Oral delivery evaluated in preclinical work
- All of these formulations suffered from PK issues
  - Low bioavailability, variability, shorter exposure times than SC injection
Nasal Target Product Profile:
- Aqueous solution formulation
- Simple manufacturing process
- Commercially available devices
- Nasal peptide products in market
- BID or TID administration

Opportunity Abandoned - un-attractive from marketing perspective
- 3 or 4X Nasal Spray required to achieve AUC equivalent to SC Injection (and clinical effect)
Transdermal Microporation Human Data (Altea)

Transdermal Target Product Profile:
• Simple bandaid-like product administered w device
• No pain on administration
• Continuous 24 hour exposure (Bydureon-like)
• Once per day administration (twice as fall back)

Opportunity Abandoned - due to significant investment requied (device, patch, manufacturing)
• Once per day 24 hour continuous exposure nearly achieved
Exenatide Lessons

- Byetta was launched in a good pen, but, with a refrigeration pack
  - CMC post-approval supplement required to get RT for 30 days
- Challenges of microsphere sustained release formulation not well understood
  - Initial interest in a once monthly product
  - Weekly product was a compromise due to initial release from particles
- Bydureon was launched in a vial and syringe
  - Importance of device was recognized too late
- Bydureon dual chamber pen was difficult and took too long
  - At launch, inferior to other weekly GLP-1 products on the market
- Bydureon MS suspension could have been completed earlier ($!)
- Decision to build MS plant instead of working with CMOs ($$$)
- Singular focus on MS investment prevented other meaningful approaches
Activities Required to Achieve Target Product Profile

Lead Molecule Selection
- Analytical Research
- Development Assessment
- Lead Molecule Design

Delivery System Selection
- Analytical Development
- Delivery System Feasibility
- Preformulation
- Formulation PK Screening

Drug Product Development
- Formulation Development
- Analytical Methods Qualification
- Development Stability
- Process Development Scale Up
- Device Selection and Development
- Technology Transfer GMP Mfg

Test Article Supply for Preclinical and Toxicity Studies

Molecule Design
- Peptide, protein variants
- Conjugates for half-life

Delivery System Design
- Aqueous or non-aqueous vehicle
- Sustained release formulation
- Triggered or targeted systems

Drug Product Design
- Pen, auto-injector
- Pre-filled syringe
- Nasal, ocular drops or spray
Take Home Message for Drug Product Development

Integration of molecular properties, formulation, and device is key to achieving the desired product profile.

Product use and self-administration constraints drive device configuration, formulation design, molecular properties.
Have Fun and Ask Questions
GLP-1 Agonist Molecular Engineering

**Twice Daily Injection**
- Exendin-4
- Lixisenatide
- Liraglutide

**Once Daily Injection**
- Ex-4 plus poly Lys
- 97% homology to GLP-1

**Once Weekly Injection**
- Albiglutide
- Semaglutide
- Dulaglutide

- GLP-1 dimer
- Lira plus optimized Albumin binder
- Two GLP-1s on Fc fragment

CARhodes GSK-CRS 18APR2017
**Liraglutide and Semaglutide**

- Lipidated GLP-1 analogues based on Novo lipidation system
- Liraglutide is 97% homologous to GLP-1
- Albumin binding by lipid for half-life extension
- Semaglutide has an optimized albumin binding side chain

**Liraglutide**
- Approved EU 2009 / US 2010
- Daily SC injection
- 1.2 to 1.8 mg per dose

**Semaglutide**
- NDA 2016
- Weekly SC Injection
- 1-2 mg per dose

1 mg at steady state