Outline

- Peptides and the Need for Delivery Technology
- Complexity of Delivery Systems
- Importance of Clinical Testing
- Life Cycle Management for Exenatide
- Challenges of Technology Development
- Program Decisions
Peptides and Delivery Needs

- Typically water soluble > 1 mg/ml
- Stability in solution is often limited (2-8C storage)
- Half-life typically 1 to 2 hrs (multiple daily injection)
- Immunogenicity a concern and needs study
- First drug product is usually solution for injection
- Life cycle interest in non-injection / sustained release injection
Combination Product Complexity

Molecule
- Efficacy / side effects
- Continuous/pulsatile
- Cost per gram
- Physchem property

Formulation
- Process complexity
- Bioavailability
- Cost per unit
- Drug compatibility

Device
- Device complexity
- Ease of use by patient
- Cost per unit
- Formulation compatibility

Biology & Chemistry
Formulation and PK
Device & Handling
Common Challenges for Novel Delivery Technologies

- Compatibility of drug, formulation, device
- Predictability of in vitro and in vivo methods
- Variability in Exposure (Cmax, AUC, Tmax)
- Cost (drug, device, formulation, manufacturing)
- Maturity of the technology (commercial or clinical?)
- Scale up experience, manufacturing systems
- Regulatory experience and acceptance
Primary Drivers for Early Clinical Testing of Delivery Sys

- Compatibility of drug, formulation, device
- Predictability of in vitro and in vivo methods
- Variability in Exposure (Cmax, AUC, Tmax)
- Overall cost of the system (drug, device, form.)
- Maturity of the technology (commercial or clinical?)
- Scale up experience, manufacturing systems
- Regulatory experience and acceptance
Case Study: Exenatide Life Cycle

- **Byetta** twice daily injection – US 2005 / EU 2006
  - Exenatide development initiated 1996
- **Bydureon** once weekly MS – EU 2011 / US 2012
  - Microsphere development initiated 2000
- **Bydureon** monthly microsphere - in development
- **Non-invasive evaluation** – preclinical and clinical
- **Transdermal patch evaluation** – preclinical and clinical
  - Transdermal program initiated 2009, clinical study 2011
Byetta Launched in 2005
Amylin-Lilly Partnership

Exenatide
Drug substance
39 amino acid peptide

Exenatide Formulation and Container Closure
1.2 & 2.4mL cartridge for injection
0.25 mg/mL strength
Acetate buffer pH 4.5, mannitol, metacresol preservative

Exenatide Disposable Pen Injector
5 mcg or 10 mcg per injection
30 day RT storage (60 injections)
GLP-1s Move to Maximize Continuous Exposure

Exenatide (Byetta) -0.9%

Liraglutide (Victoza) -1.2%

Exenatide MS (Bydureon) -1.5%


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

2015 CRS Panel Delivery Tech and Clin Devel
Exenatide Microsphere Life Cycle Extensions

- **Bydureon**
  - EU 6/2011 / FDA 1/2012 (subm. 5/2009)
  - Once weekly PLGA microsphere
  - Launched as vial and syringe
  - Complex reconstitution procedure

- **Bydureon Pen Weekly Injection**
  - FDA 3/2014
  - Dual chamber cartridge
  - Dry microspheres / diluent
  - Improved steps for handling

- **Bydureon Ready to Use Suspension Weekly Injection**
  - Microspheres in non-aqueous suspension
  - Phase 3 completed 2014 / Submit in 2015

- **Bydureon Ready to Use Suspension Monthly Injection**
Alternative Delivery Options?
Non-Invasive Exenatide

- Potentially very large market
  - Pushing product into earlier diabetes continuum
  - Larger patient population, general practitioner market

- Non-invasive systems
  - Multiple Daily Oral, Nasal, Pulmonary
  - Evaluated in preclinical, nasal clinical study, not pursued

- Transdermal System
  - Potential for extended exposure from a bandaid-like patch
  - ‘Non-invasive’ with continuous exposure efficacy
  - Evaluated preclinically, clinical study, not pursued
Exenatide Nasal Clinical Study and Conclusions

Results
- Safe and well tolerated
- Cmax 15-30 min
- Variability high
- Bioavailability 1-2%

Conclusions
- Variability too high
- 2X – 3X per day needed for Byetta like efficacy
- Decision to halt program

Presented at American Diabetes Association Meeting 2006
Exenatide Transdermal Clinical PK and PD Data

- Safe and well tolerated when administered over a 24 hour period
- Glucose AUC(0-24 hrs) was 31% for TDP versus 25% for SC Injection
- Bioavailability 3% versus SC injection

Presented at the Diabetes Technology Society Meeting
San Francisco, California   October 28, 2011
Exenatide Transdermal
Conclusions

- Technical success
  - Promising Clinical Formulations identified
  - Acceptable results for proceeding

- Economic analysis
  - Significant technology investment required
  - Questionable value for a single molecule
  - Oral once daily DPPIV had launched

- Regulatory uncertainty for approvability
  - Complex delivery technology with no direct precedent

- Program was halted
Begin with the End in Mind: Think the System Through

**Molecule**
- PKPD profile will impact formulation and device options
- Molecular properties will limit formulation options

**Formulation**
- Device and handling often dictate formulation
- Desired product profile may limit formulation options

**Device**
- Try to define the market requirements for delivery system
- Patient and physician and payor impact
- Cost of the system

**Biology & Chemistry**

**Formulation and PK**

**Device & Handling**
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