Novel Transdermal - Regulatory Landscape and Glucose Sensing and Insulin Delivery

Christopher A. Rhodes, Ph.D. President and CEO
Outline

- Novel Transdermal Technologies
  - Microporation technology
  - Exenatide case study
  - Regulatory Landscape

- Glucose Sensing Technologies
  - Rationale for glucose responsive insulin
  - History of glucose sensing
  - Boronic acid fluorescence sensors
  - Triggered insulin release programs
    - Merck (phase 1), Sensulin (preclinical development), Langer group / MIT
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)
- Overall cost of the system
  - Bioavailability, cost of components
- Maturity of the technology
  - Scale up experience, manufacturing systems
- Regulatory experience and acceptance
Mucosal Transport of Biomolecules is Limited

- Passive diffusion across mucosal barriers low
  - Permeation significant across pulmonary epithelial lining
- Permeation enhancers typically needed
  - Nasal, oral, buccal, sublingual
- Transdermal systems typically involve an active transport or membrane disruption mechanism
  - Microneedles
  - Poration
  - Iontophoresis
Case Study: Exenatide Life Cycle

- Byetta
  - Twice a day injection
- Bydureon
  - Once weekly microsphere
- What’s next?
Exenatide
Drug substance
39 amino acid peptide

Exenatide Injection
1.2 & 2.4mL cartridge for injection
0.25mg/mL strength

Exenatide Disposable Pen-injector
5 mcg or 10 mcg per injection
1.2 mL Demonstration pen
GLP-1s Move to Maximize Continuous Exposure

Exenatide (Byetta)

-0.9%

HbA1C Reduction

-1.2%

-1.5%


Liraglutide (Victoza)

T½: ~13 (9–15) h

Exenatide MS (Bydureon)

Adapted from Ellerbrand et al. Diabetes Care 2002;25:1392–1404. (n=6 for each dose)

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

14MAY2015 Drug Delivery Strategy
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

- **Non-invasive systems**
  - Multiple Daily Oral, Nasal, Pulmonary
  - Evaluated in preclinical, nasal clinical study, not pursued
  - See backup slides for more information

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

- **Transdermal System**
  - Potential for extended exposure from a bandaid-like patch
  - ‘Non-invasive’ with continuous exposure efficacy
Choice of Transdermal Program

- Altea had an attractive electroporation system
  - Atlanta based company (now Nitto Denko owns)
  - Phase 1 completed with insulin
- Opportunity to develop a 24 hour continuous patch
- Altea Passport Patch Development Agreement
  - Patch formulation for exenatide
  - Device design and development
  - Patch configuration development
  - Commercial manufacturing systems
Development Risks Identified

- Exenatide 24 hour once daily patch
  - Uncertain until formulation work complete
- Device and patch under development
  - Configuration sub-optimal, work needed
- Manufacturing systems / suppliers under-developed
  - Patch and device supplier need to be developed
  - New materials for pharmaceutical device-drug product
- Approvability uncertain
  - No product precedent approved, but, some in development
  - Safety related to immunogenicity (resolvable with phase 2b)
- Decision was made to proceed despite concerns
  - Potential commercial value significant
  - Patch form of GLP-1 delivering Bydureon-like efficacy
Application Process for Altea Passport Patch

Place patch on charged device, expose filament

Apply against skin, Activate current for msec pulse, Remove device leaving patch

Fold formulation over pores leaving ‘bandaid’
Altea Prototype System

Electronic device:
Delivers inductive current to filament

Patch system:
Adhesives / layers house disposable filament and formulation / ‘bandaid’

Challenges
• Size of device / components
  • Patch application confusing
  • Pealing off multiple layers
  • Folding over formulation onto pores
• Multiple MFG partners and unique suppliers
• Regulatory risk of approval
Transdermal Program

- Develop exenatide polymer formulation
  - Optimize for continuous 24 hour exposure (designed for maximum efficacy)
  - Consider minimally acceptable 2X per day application
- Test in hairless rats for PK
  - Identify formulations and poration conditions
  - Optimize bioavailability and onset and duration of exposure
- Develop device
  - Reduce size and improve handling by patients
  - Develop manufacturing process and suppliers
- Develop patch
  - Improve handling and application process
  - Develop manufacturing process and suppliers
- Proof of feasibility
  - Test formulation in human PK study
Exenatide Transdermal Development Program

**Formulation**
- Initial PK Feasibility: Altea
  - Optimize PK to Extend Exposure at Good BA
    - Monitor process integrity
      - Stability prototypes

**Patch**
- Identify Poration Intensity
  - Pore Density, Patch Size: Altea

**Device**
- Minimize device size and improve patient handling: Ideo
Parallel Development and Inter-related Uncertainties

- Formulation identity – Go No Go for proceeding
- Device and patch configuration – commercial implications for patient acceptance
- Manufacturing systems and suppliers – implications for COGs
- Integration challenge – moving parts have an impact on one another
- Importance of market timing – causes parallel development of formulation, device, patch
Exenatide Release and PK

Figure 1. (Top) Exenatide released into PBS from extended-release transdermal film over 24 hours. (Bottom) Exenatide pharmacokinetics in the hairless rat after microporation and 24 h application of extended-release transdermal film.

Figure 2. (Top) Exenatide released into PBS from rapid-release transdermal film over 24 hours. (Bottom) Exenatide plasma in the hairless rat after microporation and 24 h application of rapid-release transdermal film.
New and Improved Altea Device and Patch System

- Preclinical proof of concept
- Device and patch optimized with IDEO for ease of handling by 55+ year old diabetic
- Patch redesigned with Cambridge Consultants for simplified application
- Manufacturing partners for supply chain identified (device, formulation / patch)
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**
  - Formulations identified and tested in rodents
  - Acceptable results for proceeding

- **Economic analysis**
  - Awareness of significant 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**
Uncertainty for approvability
- Complex delivery technology with no direct precedent
- Chronic conditions requiring long term safety for administration

Microneedles now in late stage development
- Zosano phase 3 - metal microneedle coated with PTH
- Radius phase 3 – plastic microneedle coated with PTH
- Much simpler systems in many ways

Technical challenges for microneedle programs
- Manufacturing process for the needle array
- Coating process for the drug onto the array – requires a concentrated viscous solution
- Stability of the drug in concentrated solution
- Sterility of the process and or product required – Zosano is aseptic
- How do you clean microneedle surfaces prior to drug loading? Metal fragments?
- New and dedicated manufacturing facility

CMC complexity will raise many new questions
- Expect long review cycle with lots of detailed questions
Glucose Sensing, Triggered Release, and Insulin Delivery

- Rationale for glucose responsive insulin
- History of glucose sensing
- Boronic acid fluorescence sensors
- Triggered insulin release programs
  - Merck (phase 1)
  - Sensulin (preclinical development)
  - Langer group / MIT
  - JDRF request for proposal mid 2014
Life With Type 1 Diabetes

Basal Insulin injection in the morning

3-6 prandial (mealtime) injections at every meal / snack

3-10 lancets/day to prepare a drop of blood for glucometer
Challenges of Managing Diabetes with Insulin

- Insulin is often under or over-dosed
  - No perfect product under all conditions
  - Several different PK profiles
  - Mealtime insulin, fast-acting, ultra-fast
  - Basal insulin, once or twice per day injection

- Insulin need is variable based on physiology
  - State of your health
  - Exercising or not
  - Diet and calories taken in at recent meal
Blood Glucose Variability in Patients is Significant

- Blood glucose is regulated by insulin in a healthy people.
- Type 2 patients have started to lose Beta cell function or insulin sensitivity.
- Type 1 patients need externally administered insulin.

Blood glucose is regulated by insulin in a healthy person. Type 2 patients have started to lose Beta cell function or insulin sensitivity. Type 1 patients need externally administered insulin.
Insulin Short and Long Term Complications

- Significant risks of insulin over or under-dosing
  - Drug is injected and eliminated based on a PK profile that ranges from 2-3 hrs (meal time) to 12 to 18 hrs (basal)

- Hypoglycemia is often fatal, particularly at night
  - Last insulin dose often taken at evening meal
  - Patient is covered well for a few hours
  - However, insulin dose is too high when they go to sleep
  - Insulin has not yet cleared and drops blood glucose

- Long term issues associated with elevated glucose
  - Foot and other ulcers, blindness, heart disease, etc…
Insulin Therapy is Complicated by PK and Varying Needs

- Significant risks of insulin over or under-dosing
  - Drug is injected and eliminated based on a PK profile that ranges from 2-3 hrs (meal time) to 12 to 18 hrs (basal)
Potential for a Glucose Responsive Insulin

- The goal is for insulin release in response to blood glucose level
- Some Type 1 patients achieved control with devices
  - Pump and glucose sensor combination, often called the ‘artificial pancreas’
Insulin Pumps and Glucose Sensors On Market

1979 Yale University Professors Develop first Insulin Pump

MiniMed launches pump in 1983
MiniMed launches glucose sensor 2005
Founded by Al Mann in 1979
Medtronic purchased in 2001
## Insulin Pumps Market 2015

**Table of Insulin Pumps**

<table>
<thead>
<tr>
<th>Brand/Model</th>
<th>Size/Weight</th>
<th>Battery</th>
<th>Insulin Set</th>
<th>Insulin Type</th>
<th>Cartridge Size</th>
<th>Cartridge Capacity</th>
<th>Basal Rate</th>
<th>Bolus Rate</th>
<th>CGM Integration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animas Corp. Vibe</td>
<td>3 x 1.7 x 0.63 in.</td>
<td>314 mL, with full reservoir</td>
<td>30 mL, with certified cartridges</td>
<td>30 mL, with certified cartridges</td>
<td>No</td>
<td></td>
<td>0 to 8 units per hour</td>
<td>0 to 30 units per hour</td>
<td>Yes, can switch to regular insulin</td>
<td>No</td>
</tr>
<tr>
<td>Animas Corp.</td>
<td>2 x 2.5 x 0.88 in.</td>
<td>2.97 in. x 2.97 in. x 3.25 in.</td>
<td>515 mL, with AA batteries</td>
<td>515 mL, with AA batteries</td>
<td>From 0.05 to 25 units/12 hours</td>
<td>From 0.05 to 25 units/12 hours</td>
<td>Yes, can switch to regular insulin</td>
<td>Yes, can switch to regular insulin</td>
<td>No</td>
<td>Yes, works as stand-alone CGM</td>
</tr>
<tr>
<td>Aetina Corp.</td>
<td>3 x 1.7 x 0.63 in.</td>
<td>314 mL, with full reservoir</td>
<td>30 mL, with certified cartridges</td>
<td>30 mL, with certified cartridges</td>
<td>No</td>
<td>No</td>
<td>0 to 20 units per hour</td>
<td>0 to 20 units per hour</td>
<td>Yes, can switch to regular insulin</td>
<td>No</td>
</tr>
<tr>
<td>Medtronic Diabetes</td>
<td>Model 570G</td>
<td>5.5 x 4.4 x 1.2 in.</td>
<td>4.4 in. x 1.2 in.</td>
<td>4.4 in. x 1.2 in.</td>
<td>From 0.05 to 20 units/24 hours</td>
<td>From 0.05 to 20 units/24 hours</td>
<td>Yes, can switch to regular insulin</td>
<td>Yes, can switch to regular insulin</td>
<td>No</td>
<td>Yes, works as stand-alone CGM</td>
</tr>
<tr>
<td>Medtronic Diabetes</td>
<td>Model 640G</td>
<td>5.5 x 4.4 x 1.2 in.</td>
<td>4.4 in. x 1.2 in.</td>
<td>4.4 in. x 1.2 in.</td>
<td>From 0.05 to 20 units/24 hours</td>
<td>From 0.05 to 20 units/24 hours</td>
<td>Yes, can switch to regular insulin</td>
<td>Yes, can switch to regular insulin</td>
<td>No</td>
<td>Yes, works as stand-alone CGM</td>
</tr>
</tbody>
</table>

*CGM: Continuous Glucose Monitoring.

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**Related Resources**


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14MAY2015 Drug Delivery Strategy
## Continuous Glucose Monitors Market 2015

<table>
<thead>
<tr>
<th>Company/Country</th>
<th>Glucose Monitor</th>
<th>Transmission</th>
<th>Receiver Size</th>
<th>Battery</th>
<th>Range</th>
<th>Wearable Sensor</th>
<th>Memory</th>
<th>Pump Integration</th>
<th>Software</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anionix</strong></td>
<td>Alpha</td>
<td>2.1.5.3 or 2.5m</td>
<td>0.3cm with sensor</td>
<td>2.1.5.3 or 2.5m</td>
<td>0.3cm with sensor</td>
<td>2.1.5.3 or 2.5m with sensor</td>
<td>2.1.5.3 or 2.5m</td>
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<td>2.1.5.3 or 2.5m</td>
<td>2.1.5.3 or 2.5m</td>
</tr>
<tr>
<td><strong>Dexcom</strong></td>
<td>G6 Platinum</td>
<td>2.1.5.3 or 2.5m</td>
<td>0.3cm with sensor</td>
<td>2.1.5.3 or 2.5m</td>
<td>0.3cm with sensor</td>
<td>2.1.5.3 or 2.5m with sensor</td>
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<td>2.1.5.3 or 2.5m</td>
<td>2.1.5.3 or 2.5m</td>
</tr>
<tr>
<td><strong>Medtronic</strong></td>
<td>GuardianLink™</td>
<td>2.1.5.3 or 2.5m</td>
<td>0.3cm, without sensor</td>
<td>2.1.5.3 or 2.5m</td>
<td>0.3cm, without sensor</td>
<td>2.1.5.3 or 2.5m, without sensor</td>
<td>2.1.5.3 or 2.5m</td>
<td>2.1.5.3 or 2.5m</td>
<td>2.1.5.3 or 2.5m</td>
<td>2.1.5.3 or 2.5m</td>
</tr>
<tr>
<td><strong>Medtronic</strong></td>
<td>Reveal™</td>
<td>2.1.5.3 or 2.5m</td>
<td>0.3cm, without sensor</td>
<td>2.1.5.3 or 2.5m</td>
<td>0.3cm, without sensor</td>
<td>2.1.5.3 or 2.5m, without sensor</td>
<td>2.1.5.3 or 2.5m</td>
<td>2.1.5.3 or 2.5m</td>
<td>2.1.5.3 or 2.5m</td>
<td>2.1.5.3 or 2.5m</td>
</tr>
<tr>
<td><strong>OmniPod</strong></td>
<td>EROS™</td>
<td>2.1.5.3 or 2.5m</td>
<td>0.3cm, without sensor</td>
<td>2.1.5.3 or 2.5m</td>
<td>0.3cm, without sensor</td>
<td>2.1.5.3 or 2.5m, without sensor</td>
<td>2.1.5.3 or 2.5m</td>
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</table>


**Diabetes Forecast March/April 2015**

14MAY2015 Drug Delivery Strategy
Why Glucose-Responsive Insulin?

- Many pumps and sensors on market
- Type 2 patients don’t use them
- Type 1 patients still have swings in glucose

Enzymatic methods commonly used and incorporated into continuous sensor catheter

Glucose sensors: a review of current and emerging technology.
Oliver NS1, Toumazou C, Cass AE, Johnston DG.
Glucose Sensing Formulations

- Boronic acid binds glucose
- Also a number of other device based options

![Diagram showing boronic acid binding to glucose](image)
Glucose Sensing Formulations

- Triggered insulin release programs
  - Merck (phase 1)
  - Sensulin (preclinical development)
  - Langer group / MIT
  - JDRF request for proposal mid 2014

- Insulin formulation injected
  - Mechanism incorporated for glucose sensing
  - Glucose binding triggers release of insulin
Boronic Acid Use in Fluorescence Sensors

- Significant work on fluorescence sensing over last 20 years
- Sensors can be incorporated into formulations

A Glucose-Selective Molecular Fluorescence Sensor†
Dr. Tony D. James, Dr. K. R. A. Samankumara Sandanayake and Prof. Seiji Shinkai*
Angewandte Chemie International Edition in English
Volume 33, Issue 21, pages 2207–2209, November 17, 1994

Progress in Boronic Acid-Based Fluorescent Glucose Sensor
Hao Fang, Gurpreet Kaur, Binghe Wang
Sensulin’s Agglomerated Vesicle Technology (AVT) can deliver drugs upon various stimuli, by cross-linking drug-containing liposomes with stimulus-responsive links.

**AVT’s first application --- glucose-responsive insulin**

1. Injection of 200-400nm insulin containing particles (Subcutaneous)
2. A depot is formed, which slowly releases encapsulated insulin
3. After glucose challenge, linkers competitively bind to glucose
4. Insulin release rate increases, proportional to the level of glucose
5. When the stimulus subsides, the links re-form; release rate drops
How Does Sensulin Glucose-Responsive Insulin Work?

1. Surface Liposomes: Release Insulin First – Several will be cleaved via glucose challenges

2. Mid-Layer Liposomes: Believed to release insulin thereafter

3. Innermost / Core Liposomes: Last to release insulin

4. Insulin payload fully depleted in 24hrs, AVT liposomes believed to break down via macrophage action
## Sensulin Proof of Concept

*Glucose-Responsive Control in Diabetic Rats*

*Published in International Journal of Nanomedicine 2007:2(3) 501-513*

**Black Line:** (Control + Glucose - No AVT) Diabetic Sprague-Dawley rats, glucose bolus @ 90, 220min

**Blue Line:** (AVT only - no glucose) No Hypoglycemia in AVT/non-bolus animals

**Red Line:** (Key Experiment: AVT + Glucose) Glucose Bolus at 90 & 220 minutes results in smaller excursions in treated animals = **robust glycemic control without hypoglycemia**
- Novel Transdermal Technologies
  - Microporation technology
  - Exenatide case study
  - Regulatory Landscape
- Glucose Sensing Technologies
  - Rationale for glucose responsive insulin
  - History of glucose sensing
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BACKUP SLIDES
Properties of Peptides

• Typically water soluble > 1 mg/ml
• Stability in solution is often limited
  • hydrolysis, deamidation
  • Store in lyophilized form, or store in solution at 2-8C
• Stability as solid is good when water content is low
• Peptides < 4000 g/mol – peptide synthesis
• Peptides > 4000 g/mol – usually recombinant manuf
• Immunogenicity and safety
  • Naturally derived peptides are typically risk reduced because safety of the class is well understood
  • Immunogenicity is a concern
• Drug product is usually solution for injection
Peptide Products: Combination Products with Trivalent Complexity

**Molecule**
- Efficacy / side effects
- Continuous or pulsatile
- Cost per gram
- Physicochemical properties

**Delivery System**
- Process complexity
- Bioavailability
- Cost per unit
- Compatibility with molecule

**Device**
- Device complexity
- Ease of use / acceptance
- Cost per unit
- Formulation compatibility

**Biology & Chemistry**

**PK & Formulation**

**Device & Handling**

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Diabetes Market 2005-6 Injectable Insulin / Orals

New product options?
- Long-acting
- Non-invasive


1922

- Sulfonylurea
- Metformin
- Glitazones
- Lispro
- Aspart
- Exenatide
- Pramlintide
- Detemir
- GLP-1 analogs
- DPP – 4

14MAY2015 Drug Delivery Strategy
Non-Invasive Drug Delivery Systems

Nasal spray product
- Aqueous solution formulation
- Simple manufacturing process
- Commercially available device
- Nasal peptide products in market
- BID or TID administration

Pulmonary inhalation product
- Dry powder formulation
- Spray dry manufacturing process
- Alkermes or Nektar device
- Insulin products near market
- BID or TID administration
Nasal Exenatide Exposure in Humans

Plasma exenatide peaked at 15-30 min vs. 2 hours with SC
Exenatide Nasal Conclusions

- Formulations identified and tested in rodents and primates
- Two formulations tested in humans
- Human bioavailability low but not primary issue
- Variability in exposure too high at peak
- Byetta like efficacy was achievable with two to three nasal sprays per day
- Program was halted