Challenges and Opportunities for Parenteral to Oral Switch for Peptide Therapeutics: Case Study on Buccal Delivery Using Mucoadhesive Films

Nozer Mehta, VP Biologics
MonoSol Rx

AAPS Short Course 3: Assessing and Applying Enabling Delivery Technologies and Formulation Tools to Oral Small Molecule (BCS II/IV) and Peptide Therapeutics (BCS III)
2015 AAPS Annual Meeting, Orlando, Fla.
Outline

- Oral (enteral) delivery as non-invasive route for chronic administration - Advantages and issues
- Brief overview of oral delivery technologies
- Recent approvals for peptide therapeutics
- Recent NDA filings for orally delivered peptides
  - Chiasma Oral Octreotide
  - Tarsa Oral Calcitonin
- Advantages of mucoadhesive buccal films for oral peptide delivery (PharmFilm® technology)
  - Formulation development and pre-clinical studies with orally soluble buccal films
## Recent U.S. Peptide Therapeutic Approvals

<table>
<thead>
<tr>
<th>Peptide Name</th>
<th>Brand name</th>
<th>Company</th>
<th>Date of Approval</th>
<th>Approved Indications</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide (31 aa)</td>
<td>Saxenda</td>
<td>Novo Nordisk</td>
<td>December-14</td>
<td>Obesity</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Dulaglutide (46 aa)</td>
<td>Trulicity</td>
<td>Eli Lilly &amp; Co</td>
<td>September-14</td>
<td>Type 2 diabetes</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Albiglutide (60 aa)</td>
<td>Tanzeum</td>
<td>GlaxoSmithKline</td>
<td>April-14</td>
<td>Type 2 diabetes</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Teduglutide (33aa)</td>
<td>Gattex</td>
<td>NPS Pharmaceuticals</td>
<td>December-12</td>
<td>Short bowel syndrome</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Linaclotide (14 aa)</td>
<td>Linzess</td>
<td>Ironwood Pharmaceuticals</td>
<td>August-12</td>
<td>Treatment of chronic idiopathic constipation and to treat irritable bowel syndrome with constipation (IBS-C) in adults</td>
<td>Oral</td>
</tr>
<tr>
<td>Carfilzomib (4 aa)</td>
<td>Kyprolis</td>
<td>Onyx Pharmaceuticals</td>
<td>July-12</td>
<td>Multiple Myeloma</td>
<td>Intraveneous</td>
</tr>
<tr>
<td>Pasireotide (8 aa)</td>
<td>Signifor</td>
<td>Novartis</td>
<td>April-12</td>
<td>Cushing’s Disease, Acromegaly</td>
<td>Intramuscular</td>
</tr>
<tr>
<td>Peginesatide</td>
<td>Omontys</td>
<td>Takeda</td>
<td>March-12 removed from market in February-13</td>
<td>Anemia</td>
<td>Intraveneous</td>
</tr>
</tbody>
</table>

From Janice Reichert, Reichert Biotechnology Consulting
### Recent Peptide Therapeutics in Late Stage Development

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Company</th>
<th>Therapy Area</th>
<th>Indications</th>
<th>Product Stage</th>
<th>Recent News</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Glargine &amp; Lixisenatide</td>
<td>Sanofi</td>
<td>Endocrine</td>
<td>Type 2 diabetes</td>
<td>Pre-Registration</td>
<td>NDA submitted to FDA</td>
</tr>
<tr>
<td>Etelcalcetide</td>
<td>Amgen Inc.</td>
<td>Metabolic Disorders</td>
<td>Secondary Hyperparathyroidism</td>
<td>Pre-Registration</td>
<td>NDA submitted to FDA</td>
</tr>
<tr>
<td>Selepressin</td>
<td>Ferring International Center S.A.</td>
<td>Other Diseases</td>
<td>Septic Shock</td>
<td>Phase III</td>
<td>NCT02508649 Phase 3 started in July 2015</td>
</tr>
<tr>
<td>CR-845</td>
<td>Cara Therapeutics, Inc.</td>
<td>Central Nervous System</td>
<td>Post-Operative Pain</td>
<td>Phase III</td>
<td>NCT02542384 Phase 3 started in Sep 2015</td>
</tr>
<tr>
<td>Forigerimod Acetate</td>
<td>Immupharma Plc</td>
<td>Immunology</td>
<td>Systemic Lupus Erythematosus</td>
<td>Phase III</td>
<td>NCT02504645 Phase 3 study in SLE due to start in Sep 2015 not yet recruiting as of Oct 5</td>
</tr>
<tr>
<td>GBT-201/RGN-259</td>
<td>RegeneRx Biopharmaceuticals, Inc.</td>
<td>Ophthalmology</td>
<td>Keratitis; Keratoconjunctivitis sicca (Dry Eye)</td>
<td>Phase III</td>
<td>Phase 3 to start according to licensee G-treeBNT</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>Novo Nordisk</td>
<td>Endocrine</td>
<td>Type 2 diabetes</td>
<td>Phase III</td>
<td>Completed one Phase 3, 5 more scheduled</td>
</tr>
<tr>
<td>Semaglutide (oral)</td>
<td>Novo Nordisk</td>
<td>Endocrine</td>
<td>Type 2 diabetes</td>
<td>Phase II</td>
<td>To enter Phase 3 in 2016</td>
</tr>
<tr>
<td>ITCA-Exenatide</td>
<td>Intarcia</td>
<td>Endocrine</td>
<td>Type 2 diabetes</td>
<td>Phase III</td>
<td>Continuous subcutaneous delivery, completed 3 of 4 Phase 3 trials</td>
</tr>
</tbody>
</table>

From Janice Reichert, Reichert Biotechnology Consulting
Therapeutic receptor targets for peptides in clinical studies

Kaspar and Reichert 2013. Drug Discovery Today Volume 18, Numbers 17/18
# GLP-1 Receptor Agonists in Clinical Development

## Table 1

<table>
<thead>
<tr>
<th>Company</th>
<th>Peptide name</th>
<th>Development stage</th>
<th>Target</th>
<th>Dosing regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lilly</td>
<td>Cpd86</td>
<td>Preclinical</td>
<td>GLP-1/GIP</td>
<td>SC, once daily</td>
</tr>
<tr>
<td>Zealand Pharma</td>
<td>ZP2929</td>
<td>Phase I</td>
<td>GLP-1/GCG</td>
<td>SC, once daily</td>
</tr>
<tr>
<td>Zealand Pharma</td>
<td>ZP3022</td>
<td>Preclinical</td>
<td>GLP-1/GLP-2/CCKB</td>
<td>SC, once daily</td>
</tr>
<tr>
<td>Prolor (Opko Biologics)</td>
<td>MOD-6030</td>
<td>Preclinical</td>
<td>GLP-1/GCG</td>
<td>SC, once daily</td>
</tr>
<tr>
<td>Hamni Pharmaceuticals</td>
<td>HM12525A</td>
<td>Phase I</td>
<td>GLP-1/GCG</td>
<td>SC, once weekly</td>
</tr>
<tr>
<td>Diartis Pharmaceuticals</td>
<td>VSR859</td>
<td>Phase I</td>
<td>GLP-1</td>
<td>SC, once monthly</td>
</tr>
<tr>
<td>Novo Nordisk</td>
<td>NN9926</td>
<td>Phase I</td>
<td>GLP-1</td>
<td>Oral, long acting</td>
</tr>
<tr>
<td>TransTech Parma</td>
<td>TTP273/TTP054</td>
<td>Phase II</td>
<td>GLP-1</td>
<td>Oral</td>
</tr>
<tr>
<td>Zydus-Cadila</td>
<td>ZYG1</td>
<td>Phase II</td>
<td>GLP-1</td>
<td>Oral</td>
</tr>
<tr>
<td>Roche</td>
<td>MAR709</td>
<td>Phase II</td>
<td>GLP-1/GIP</td>
<td>SC, once daily</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>TT401</td>
<td>Phase II</td>
<td>GLP-1/GCG</td>
<td>SC, once weekly</td>
</tr>
<tr>
<td>Hamni Pharmaceuticals</td>
<td>HM11260C</td>
<td>Phase II</td>
<td>GLP-1</td>
<td>SC, once weekly</td>
</tr>
<tr>
<td>PhaseBio Pharmaceuticals</td>
<td>PB1023</td>
<td>Phase II</td>
<td>GLP-1</td>
<td>SC, once weekly</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>Dulaaglutide</td>
<td>Phase III</td>
<td>GLP-1</td>
<td>SC, once weekly</td>
</tr>
<tr>
<td>Novo Nordisk</td>
<td>Semaglutide</td>
<td>Phase III</td>
<td>GLP-1</td>
<td>SC, once weekly</td>
</tr>
<tr>
<td>Intarcia</td>
<td>ITCA</td>
<td>Phase III</td>
<td>GLP-1</td>
<td>SC, once yearly</td>
</tr>
</tbody>
</table>

*a Abbreviation: SC subcutaneous.*

Advantages of Oral (Enteral) Delivery of Peptides

- Eliminates need for daily or frequent injections for chronic therapies
- Increases physician acceptance and improves patient compliance
- May eliminate the need for cold chain transport and refrigeration of the drug by the patient
- Affords opportunity for life cycle extension for approved drugs
Challenges to oral peptide delivery

- Inter-and Intra-subject variability in chronic dosing
- Potential toxicity with permeation enhancers
- Low bioavailability – cost of goods
- Limit to maximum dose that can be delivered
- Susceptibility of peptides to acid degradation and protease digestion
- Low permeability in the GI tract
- First pass metabolism
- Variability due to food effects and poor patient compliance with dosing regimen
Variability in Oral Delivery of PTH Analog

Common Molecules that are Tight Junction Modifiers

- **Drug Compounds:**
  - Aspirin
  - NSAIDS
  - Phenothiazines

- **Food and Drug Additives/Excipients:**
  - EDTA
  - C8-C18 fatty acids
  - Various polymers
  - Poly-L-lysine

- **Natural/Food Products:**
  - ZOT
  - ATP
  - Chitosan and chitosan derivatives
  - Wheat gluten
  - Oat saponins
  - Capsaicin
  - Alcohol

Enteris BioPharma Non-confidential Presentation
# Currently Approved Oral Peptide Drugs

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Product</th>
<th>Indication</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine (1202)</td>
<td>Neoral Sandimmune®</td>
<td>Immunosuppression</td>
<td>Cyclic hydrophobic peptide</td>
</tr>
<tr>
<td>Desmopressin (1183)</td>
<td>Minrin ®</td>
<td>Nocturia</td>
<td>Soluble salt of cyclic peptide. F = 5% compared to intranasal DDAVP, and about 0.16% absolute bioavailability.</td>
</tr>
<tr>
<td></td>
<td>Minrin Melt ®</td>
<td>Diabetes insipidus</td>
<td></td>
</tr>
<tr>
<td>Glutathione (307)</td>
<td>Cachexon ®</td>
<td>AIDS-related cachexia</td>
<td>Tripeptide also found in health supplements</td>
</tr>
<tr>
<td>Linaclotide (1527)</td>
<td>Lizness ®</td>
<td>Irritable bowel syndrome</td>
<td>Cyclic peptide agonist of guanylate cyclase 2C derived from E.Coli enterotoxin</td>
</tr>
<tr>
<td>Taltirelin hydrate (477)</td>
<td>Ceredist ®</td>
<td>Spinocerebellar ataxia</td>
<td>Practically insoluble TRH analogue. For CNS</td>
</tr>
<tr>
<td></td>
<td>Ceredist OD ®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tyrothricin (1228)</td>
<td>Angiovac ®</td>
<td>Pharyngitis</td>
<td>Cyclic polypeptide, practically insoluble</td>
</tr>
<tr>
<td>Vancomycin hydrochloride (1485)</td>
<td>Vancocin ®</td>
<td>Infection</td>
<td>Tricyclic glycopeptide antibiotic, freely soluble</td>
</tr>
<tr>
<td>Colistin sulfate (1268)</td>
<td>Colomycin ®</td>
<td>Infection</td>
<td>Cyclic peptide</td>
</tr>
</tbody>
</table>

Andrew Lewis, Ipsen, CRS Workshop on Oral Peptides (2014)  
David Brayden, University College Dublin, AAPS (San Diego, 2014)
## Selected Oral Delivery Technologies

<table>
<thead>
<tr>
<th>Company</th>
<th>Lead Peptide</th>
<th>Technology Name</th>
<th>Technology composition</th>
<th>Formulation</th>
<th>Partnership</th>
<th>Current Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteris Biopharma</td>
<td>Calcitonin</td>
<td>Peptelligence</td>
<td>Absorption enhancer (acyl carnitine) and enzyme inhibitor (organic acid: citric acid)</td>
<td>Tablet</td>
<td>Tarsa Therapeutics</td>
<td>Phase III</td>
</tr>
<tr>
<td>Chiasma</td>
<td>Octreotide</td>
<td>TPE</td>
<td>Suspension of drug particles in oils and absorption enhancer (caprylic acid, C8, castor oil, medium chain)</td>
<td>Capsule</td>
<td>Roche (discontinued)</td>
<td>Phase III</td>
</tr>
<tr>
<td>Oramed</td>
<td>Insulin and exenatide</td>
<td>POD</td>
<td>Peptide with absorption enhancer (e.g. EDTA) and protease inhibitors (e.g. soya bean trypsin inhibito, EDTA) enteric coated tablet/capsule</td>
<td>Capsule</td>
<td>Novartis</td>
<td>Phase II</td>
</tr>
<tr>
<td>Merrion Pharmaceuticals</td>
<td>Insulin and GLP-1 analogues</td>
<td>GIPET</td>
<td>Absorption enhancer : medium chain fatty acids (sodium caprate) as a</td>
<td>Tablet</td>
<td>NovoNordisk</td>
<td>Phase I</td>
</tr>
<tr>
<td>Emisphere</td>
<td>Insulin and GLP-1 analogues</td>
<td>Eligen</td>
<td>Absorption enhancers SNAC, SNAD, 5-CNAC</td>
<td>Tablet</td>
<td>Novo Nordisk</td>
<td>Phase I &amp; II</td>
</tr>
<tr>
<td>Nod Pharmaceuticals</td>
<td>Insulin</td>
<td>NOD</td>
<td>Bioadhesive calcium phosphate nanoparticles</td>
<td>Capsule</td>
<td></td>
<td>Phase I</td>
</tr>
<tr>
<td>Midatech</td>
<td>Insulin and GLP-1 analogues</td>
<td>GNP/Nanocells</td>
<td>Surface modified gold nanoparticles complexed with peptides</td>
<td>Adhesive buccal patch</td>
<td></td>
<td>Phase I</td>
</tr>
<tr>
<td>Rani Therapeutics</td>
<td>Insulin and GLP 1 analogues</td>
<td>Robotic pill</td>
<td>Balloon-like structure outfitted with hollow micro needles made of sugar and preloaded with peptides.</td>
<td>Capsule made of biodegradable material (e.g. PLGA)</td>
<td>Novartis</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

Hassani, Lewis and Richard 2015. ONDrug Delivery 59:12-17
Recent NDA Applications for Orally Delivered Peptide Drugs

- Chiasma Inc. submitted an NDA to U.S. FDA for Octreotide Capsules for treatment of Acromegaly in June 2015
  - The NDA filing was accepted in August 2015

  - The NDA filing was accepted in Oct 2015
Preparation of Oral Octreotide Capsules

MCFAS = Medium Chain Fatty Acid Salts

Published in Tuvia et al, Pharmaceutical Research, 2014

Dose-response effect of oral octreotide acetate on plasma octreotide levels.

Oral Octreotide Multicenter Phase 3 Study in Acromegaly Patients

- 155 patients receiving injectable octreotide switch to oral capsule formulation
- Subjects were initially switched to 40 mg/d oral octreotide capsules (OOCs), and the dose escalated to 60 and then up to 80 mg/d to control IGF-1
- The fixed doses were then maintained for a 7-month core treatment, followed by a voluntary 6-month extension
- 65% of the subjects achieved the primary endpoint of IGF-1 < 1.3 x ULN and mean integrated GH < 2.5 ng/mL at the end of the core treatment period and 62% at the end of treatment (up to 13 mo)
- Twenty-one subjects (13.5%) experienced 39 serious AEs, of which two were considered possibly related to OOC. The authors state that overall, OOC safety was consistent with the known octreotide safety profile and acromegaly disease burden, with no new emerging safety signals related to the novel formulation and route of administration.

Peptelligence® Oral Delivery Technology

Stern et al 2015. Drug Development & Delivery No 2S:36-42
The Phase 3 Pivotal Study Design for Oral Calcitonin

The ORACAL Study: Design

- US
- UK
- Poland

→ Postmenopausal Women

- Hungary
- Bulgaria
- South Africa

- 45 years or older
- Osteoporosis at LS or Hip
- Generally healthy, vit D replete
- No recent Rx, steroids or HRT

All patients received calcium and vitamin D

- Oral rsCT + Nasal pbo
- Oral pbo + Nasal sCT
- Oral pbo + Nasal pbo
Nighttime Dosing of Oral Calcitonin Increases Efficacy

**OSTORA**: Dosing Regimen Developed to Achieve Optimal Clinical Response

Night Time Dosing Prevents Accelerated Bone Loss

Changes from Baseline CTX for Period 1 and Period 2 Subjects

OSTORA Dosed at night when bone loss is highest
Phase 3 Pivotal Study Results for Oral Calcitonin

**OSTORA** was Superior to Nasal CT and Placebo at Primary Endpoint: Lumbar Spine

![Graph showing comparison of mean % change in LS-BMD for rsCT Tablet, Nasal Spray, and Placebo.](image)

- rsCT Tablet (N=189): Mean % Change = 1.53, p<0.001*
- Nasal Spray (N=140): Mean % Change = 0.78, p=0.014*
- Placebo (N=82): Mean % Change = 0.47, p=ns*

*Compared to baseline mITT Population, LOCF
Rani Therapeutics Robotic Pill Technology

- http://www.ranitherapeutics.com/
PharmFilm® Technology Platform for Peptide Delivery

• Oral soluble film embedded with Active Pharmaceutical Ingredient
• Enteral, buccal, sublingual, routes of administration
• Technical advantages
  – Mucoadhesivity
  – Residence time (driven by dissolution rate & thickness)
  – Surface area (exposure to oral mucosa)
  – Avoids first pass metabolism
  – Improved onset of action
  – Easy to administer
  – Portable — can be taken anytime, anywhere
  – Can be taken without water
  – Can reduce GI adverse events
  – Ideal alternative for those with difficulty swallowing pills
PharmFilm Manufacturing

Two manufacturing facilities (Indiana)
80,000 sq. feet of GMP space
Multiple manufacturing lines capable of > 1 billion commercial doses

Key Levers for Content Uniformity/Dimensions
- Weight of polymers (dissolution time)
- Thickness of film (dissolution time)
- Acceptable length/width of film
- API vs. excipient ratio
**How does film work?**

- PEO (Polyethylene oxide) and other polymers are used as film formers to hold API and excipients in place.
- Patented mixing techniques are used to ensure the API is uniformly distributed throughout the film.
- Upon application to the mucosa, the PEO/other polymers and excipients begin to dissolve based on the proprietary compositional profile created during formulation.
- API is released in a rate determined by the compositional profile.

**Kinetics: Tmax & Cmax**

- Controlling the release rate allows variation of the kinetics created by various APIs or proteins.
- Sustained or quick release have a direct impact on Tmax and Cmax.
MonoSol Rx has successfully brought two products to market that leverage its proprietary PharmFilm technology.
Faster Onset of Action by Sublingual Absorption

MSRX-201, shown below, provides for a significantly faster onset of action when compared to the currently marketed product, MAXALT (rizatriptan).
## Controlling Exposure and Variability

PharmFilm for buccal or sublingual delivery provides several levers with which to control variability during the transmucosal delivery of peptides and proteins.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Consistent Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of dissolution</td>
<td>Mucoadhesion</td>
</tr>
<tr>
<td>Surface area of the film</td>
<td>Unidirectional absorption</td>
</tr>
</tbody>
</table>
Buccal Absorption

Buccal absorption can occur either through transcellular and/or paracellular transport. The pore size of the aqueous pathway is between 16 nm and 20 nm.

Permeation Enhancers

Peptide permeation can be increased by the addition of enhancers that open cell junctions, increasing cell membrane fluidity, and/or extracting intercellular lipids.

Protection from Enzymes

Peptide degradation during delivery can be prevented by altering the pH or addition of protease inhibitors.
## Polymers for PharmFilm® Evaluation

<table>
<thead>
<tr>
<th>EXCIPIENT</th>
<th>CATEGORY</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
</table>
| Pullulan      | polymer   | • Polysaccharide polymer produced from starch  
                 • Excellent film forming properties  
                 • Provides relatively rapid dissolution time                                  |
| Kollicoat IR  | polymer   | • Flexible polyvinyl alcohol/polyethylene glycol graft copolymer  
                 • Acts as dual-function: film forming polymer and plasticizer  
                 • Low viscosity, high binding efficiency, no peroxide formation, and cost efficient coating material |
| PolyOx        | polymer   | • High MW water soluble Polyethylene oxide  
                 • MonoSol Rx’s preferred polymer composition for PharmFilm® Technology       |
| Chitosan      | polymer   | • Water soluble low MW chitosan  
                 • Strong mucoadhesive property due to hydrogen and ionic bonding with mucosa  
                 • Shown to be efficient permeation enhancer                                   |
| Carbopol      | polymer   | • Homopolymer of acrylic acid crosslinked with sucrose or allyipentaerythritol  
                 • Excellent mucoadhesive property                                              |
## Permeation Enhancers for PharmFilm® Evaluation

<table>
<thead>
<tr>
<th>EXCIPIENT</th>
<th>CATEGORY</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brij58</td>
<td>enhancer</td>
<td>• Non-ionic surfactant, Polyoxyethylene (20) acetyl ether</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Enhances paracellular transport</td>
</tr>
<tr>
<td>NaCitrate</td>
<td>enhancer</td>
<td>• Chelator type enhancer, Interferes with Ca(^{2+})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Paracellular transport</td>
</tr>
<tr>
<td>GMO</td>
<td>enhancer</td>
<td>• Polar lipid surfactant type enhancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Interacts with phospholipid bilayer system and induces intercellular lipid disorder</td>
</tr>
<tr>
<td>Decanoic Acid</td>
<td>enhancer</td>
<td>• Saturated fatty acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Increases fluidity of phospholipid domain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Paracellular transport</td>
</tr>
<tr>
<td>NaGDC</td>
<td>enhancer</td>
<td>• Bile salt type enhancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Increases membrane fluidity, Perturbs intercellular lipids to increase paracellular transport</td>
</tr>
<tr>
<td>Maltitol Syrup</td>
<td>sweetener/plasticizer/ permeation enhancer</td>
<td>• Sugar alcohol used as a sugar substitute</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Used also as a plasticizer or permeation enhancer</td>
</tr>
</tbody>
</table>
### Peptide Formulation Development Pathway

**In vitro Studies**
- Excipient compatibility of peptide with polymers and enhancers
- Sensitive HPLC assay
- Small scale preparation of films to study flexibility, tensile strength, muco-adhesive properties
- Stability studies on film formulations

**Ex vivo Studies**
- EpiOral tissue model (MatTek Corporation) of human buccal epithelial tissue
- Porcine buccal explant tissue in Franz cell model
- Determination of flux and percent permeation
- Determination of MTT value and TEER

**In vivo studies**
- Studies in Yucatan mini-pig model with buccal or sublingual formulations
- Determination of PK and PD response as appropriate
### Buccal Mucosa in Mammals

#### Comparison of buccal mucosa of different mammals.

<table>
<thead>
<tr>
<th>Models</th>
<th>Tissue structure [6]</th>
<th>Buccal membrane thickness (µm) [38,39] (mean ± SD)</th>
<th>Permeability constant for tritiated water (×10^7 cm/min) [38,40] (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>Non-keratinized</td>
<td>580 ± 90</td>
<td>579 ± 122</td>
</tr>
<tr>
<td>Dog</td>
<td>Non-keratinized</td>
<td>126 ± 20</td>
<td>1045 ± 37</td>
</tr>
<tr>
<td>Hamster</td>
<td>Keratinized</td>
<td>115.3 ± 11.5</td>
<td>Not available</td>
</tr>
<tr>
<td>Pig</td>
<td>Non-keratinized</td>
<td>772 ± 150</td>
<td>634 ± 60</td>
</tr>
<tr>
<td>Rabbit</td>
<td>Partially keratinized</td>
<td>600</td>
<td>Not available</td>
</tr>
<tr>
<td>Rat</td>
<td>Keratinized</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>Monkey</td>
<td>Non-keratinized</td>
<td>271 ± 50</td>
<td>1025 ± 154</td>
</tr>
</tbody>
</table>

EpiOral Model (MatTek) for Pre-clinical Studies

Human Buccal Tissue:

- Highly organized basal cells (BC)
- Stratum Filamentosum (SF)
- Stratum Distendum (SD)
- Microporous Membrane (MM)
- Lamina Propria (LP)

EpiOral Tissue:

MatTek Corporation non-confidential slides
MTT Assay for Cell Viability

3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) 

(E,Z)-5-(4,5-dimethylthiazol-2-yl)-1,3-diphenylformazan (Formazan)

Mitochondrial Reductase
EpiOral Permeation Study: Linearity of Permeation with Octreotide Load (N=3)

Octreotide Permeation (mg) vs. Time (Hours)
- 15 mg Octreotide
- 10 mg Octreotide
- 5 mg Octreotide

Octreotide Permeation (%) vs. Time (Hours)
- 15 mg Octreotide
- 10 mg Octreotide
- 5 mg Octreotide
EpiOral Tissue Study with PharmFilm® + Bile Salt Enhancer: %Permeation of Octreotide (N=3)
Permeation of Exenatide with and without Permeation Enhancers

- 1 mg Exenatide with Bile Salt in Tris pH 7.5
- 1 mg Exenatide with Surfactant in Tris pH 7.5
- 1 mg Exenatide in Tris pH 7.5
Permeation of Exenatide in PharmFilm® + Bile Salt Enhancer in Acetate Buffer pH 5.5 (N=3)
Preclinical Study of PTH1-34 in Minipig Model: PK Results

Preclinical Study: Gottingen Minipigs

Plasma teriparatide levels (pg/mL)

Minutes Post Dosing

500mcg teriparatide PharmFilm
20mcg Forteo SQ
Preclinical Study of PTH1-34 in Minipig Model: PD Results

Serum Calcium Levels Following sc Injection of 20 mcg FORTEO in Pigs (n=4)

Serum Calcium Levels Following Sublingual Application of Three Teriparatide Films (100 mcg) in Pigs

Basal Calcium Levels: No Dose Administered

Teriparatide Film #1 (n=1)
Teriparatide Film #2 (n=1)
Teriparatide Film #3 (n=1)
Summary

- Peptides continue to generate increasing interest as treatments for a variety of therapeutic indications
- GLP-1 receptor agonists for the treatment of Type 2 diabetes are the most prevalent class of molecules
- The majority of peptide drugs are still delivered by injectable delivery routes.
- There is an intense interest in oral delivery technologies, with molecules at different stages of clinical development
  - Oral formulations of two peptide drugs, octreotide and calcitonin, are currently under NDA review
- Delivery by an orally dissolving buccal film technology offers further advantages over enteral delivery for peptide molecules for several reasons
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  - James Treubig
  - Vince Buono

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  - Chee Youb Won

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- Marketing
  - Jessica Patel
Thank you

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Manufacturing
Mixing

SCALE: Laboratory ➔ 38 kg ➔ 115 kg ➔ 380 kg ➔ 950 kg ➔ 2000 kg
Manufacturing
Coating

- Web widths: 8” ➔ 16” ➔ 23” ➔ 31”
- Very uniform drug concentration/area
- Very uniform across and along web length
- Very uniform thickness and appearance
- Bulk product is the finished product
  - Dose proportionality
Manufacturing
Content Uniformity/Dose Dimensionality

Key Levers
- Weight of polymers (dissolution time)
- Thickness of film (dissolution time)
- Acceptable length/width of film
- API vs. excipient ratio
Manufacturing
Packaging

- High Speed Pouching Machines
- Unit doses are created from bulk in pouching operation
- Foil-Foil Pouching available as CR or non-CR
- Offers moisture, light and oxygen barrier