Adare Pharmaceuticals -
A Patient-Centric Approach to Drug Formulation

Drug Delivery & Formulation Summit
Berlin, May 23-25, 2016

Holger Neecke
Director of Business Development

Luigi Boltri
Director, Innovation & Technology Liaison
Adare – a Global Specialty Pharmaceutical Company

- Acquired by TPG from Actavis in 2015
- >600 employees, ~$150 million revenues in 2014
- >40 products commercialized by partners around the world
  - Therapeutic areas of excellence include CNS and GI
- >50 years drug development experience
  - >360 patents, 225 applications
  - Solving formulation, manufacturing, commercialization challenges
- Value generation for partners: new products and line extensions
- Strong growth trajectory
  - Reformulations of APIs in oral drug delivery, suppositories, and enemas
  - Development and acquisition of new technologies and products

Adare transforms medicines, creating new possibilities for improved patient health
Established Commercial Operations in North America and Europe
World-Class R&D and Manufacturing Sites

- R&D Formulation Center of Excellence in US
- Manufacturing sites in N.A. and Europe
  - Supply global market with turnkey solutions
  - High quality cGMP facilities
  - Approved for controlled substances and solvents
  - Excellent environmental credentials

- Substantial experience in gaining regulatory approval for both US and Europe
- Success and expertise in hosting international audits from regulatory agencies, including US, Europe, Asia, Middle East and Latin America
Developing Patient-centric Dosage Forms

WE BELIEVE

No patient should have to settle for “good enough”
Patient-centric Drug Formulation Needs
Ease of swallowing and convenience

Orally Dispersible Tablet

Dry Syrup / Sprinkle

Infant Dispenser
Patient-centric Drug Formulation Needs
Mix-up Prevention and Reduction of Pill Burden

Size, shape, color differentiation for easy identification

Long acting (once a day/week/...)

“Combo” products

©2016 Adare Pharmaceuticals, Inc.
Broad Proprietary Technology Portfolio

• Distinct oral formulation technologies
  – Scaled-up and validated
  – Commercialized worldwide
  – Patent protected
• Applicable to Rx and OTC products — therapeutic area agnostic

Create patient-centric formulations: novel products and differentiation for line extensions

LIQUITARD, MICROCAPS, DIFFUCAPS, DIFFUTAB, and EURAND MINITABS are registered trademarks of Adare Pharmaceuticals S.r.l. BIORISE and ORBEXA are trademarks of Adare Pharmaceuticals S.r.l. ADVATAB is a registered trademark of Adare Pharmaceuticals, Inc.

©2016 Adare Pharmaceuticals, Inc.
Since 2009, Over 60 Product Launches in 44 Countries

All trademarks are property of their respective owners. Artists’ rendition of Lactéo® packaging. The 170 mg dose is not pictured above.
Track Record of Partnering Success

Over 40 Products Incorporating Our Proprietary Technologies Have Been Commercialized Around the World

The above corporate marks are the property of their respective owners.

©2016 Adare Pharmaceuticals, Inc.
Well Established Partnership Business Models

**Co-development Projects:**

*Technology Licensing and Product Development*

- Feasibility / Formulation Development
- Analytical Testing
- Clinical Trial Materials
- Clinical Scale-Up
- Full Scale Manufacturing

**Product License/Commercial Supply Projects**

- Product Data
- Filing
- Launch
- Full Scale Manufacturing

**Alliance and Project Management**
## Examples of Successful Formulation Developments

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Description</th>
<th>Technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fexofenadine dry sachet</td>
<td>SANOFI</td>
<td>MHLW (Japan) approved as alternative to tablets for children and adults who have difficulty swallowing</td>
<td>Microcaps®, Liquitard®</td>
</tr>
<tr>
<td>Tenofovir disoproxil oral powder/granule formulation</td>
<td>GILEAD</td>
<td>FDA / EMA approved for HIV-1 infection in children and adults unable to swallow tablets</td>
<td>Microcaps®</td>
</tr>
<tr>
<td>CNS drug ODT</td>
<td>Private partner</td>
<td>CNS drug orally disintegrating tablets FDA approved for CNS Medical Condition</td>
<td>Microcaps®, AdvaTab®</td>
</tr>
</tbody>
</table>

All trademarks are property of their respective owners. The above corporate marks are the property of their respective owners.
Microcaps® + Liquitard® Technology
Fexofenadine Case Study
**Microcaps® - Complete and Effective Taste-masking**

- **Microencapsulation by coacervation:**
  - Uniform coating of a solid particle or liquid droplet with a rigid semi-permeable polymer

- **Creates a physical barrier:**
  - Effective taste masking
  - Customized release profile
  - Turn liquids into solids
  - Combine incompatible APIs

---

**Adare is the leader in organic phase coacervation for pharmaceutical products**

©2016 Adare Pharmaceuticals, Inc.
Microcaps® - Proprietary Taste Masking Process

- Although spherical particles are shown (yellow), the Microcaps® coacervation process can be used for varying not isometric particle shapes.
Microcaps® - Proprietary Taste Masking Process (cont’d)

Core and Liquid Coating in Manufacturing Vehicle

Deposition of Liquid Coating Material

Completed Capsules in Manufacturing Vehicle
Liquitard® - Very Convenient Stick Pack Dosage Form

- Liquitard® hydrophilic powder
  - Thickening and suspending agents for homogenous suspension
  - Combine with Microcaps® taste-masked particles
- Single-dose stick pack
  - Direct dose, temporary suspension or sprinkle on easy-to-swallow foods
  - Wide variety of flavors
  - Compatible with customized release technologies
  - Dosing accuracy, portability and convenience

Improves patient convenience / encourages adherence
### Case Study I: Fexofenadine Sachets
How to Mask Unpleasant Taste for Pediatric Patients

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Fexofenadine HCl (15 and 30 mg) for symptoms of allergic rhinitis, and for uncomplicated skin manifestations of chronic idiopathic urticaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEED</td>
<td>Oro-dispersible dry syrup formulation alternative to Allegra® tablets* for pediatric administration†</td>
</tr>
<tr>
<td></td>
<td>Taste-mask a bitter API</td>
</tr>
<tr>
<td></td>
<td>Suitable to be administered:</td>
</tr>
<tr>
<td></td>
<td>✓ in 50ml of water</td>
</tr>
<tr>
<td></td>
<td>✓ onto a tablespoon with few ml of water</td>
</tr>
<tr>
<td></td>
<td>✓ directly in the mouth avoiding water intake</td>
</tr>
</tbody>
</table>

*ALLEGRA is a registered trademark of Aventisub II Inc.
†The formulation is particularly beneficial for pediatric use
Fexofenadine - Successful Microencapsulation

- Uniform coating (15% w/w ethylcellulose)
- Robust and reliable manufacturing process (~100% coating applied)
- Extremely small taste-masked particle size (PSD ~100 µm)
- DRT comparable to Allegra® tablets
Fexofenadine - Effective Taste Masking

• Effective taste-masking and no sandy effect
  – Fexofenadine HCl microcapsules (prototypes #36 and #47) show taste-masking in the same range as placebo and taste-less reference product
Fexofenadine - Successful Development + Launch in JP

• Partnered with Sanofi K.K. to deliver Allegra Dry Syrup 5% for children and adults with difficulty in swallowing

• Developed successfully from concept to product
  – Achieved successful taste masking of a bitter API
  – Can be sprinkled on easy-to-swallow foods

• Commercial presentation:
  – 300 mg / 600 mg sachet oral powder formulation using Microcaps® taste masking and Liquitard® suspension technology

• Added IP for formulation and process (expiry 2030)

• Launched in Japan in January 2015

Allegra® is a registered trademark of Aventisub II Inc.

©2016 Adare Pharmaceuticals, Inc.
Microcaps® Technology
VIREAD® for Pediatric Patients
**Case Study II: Viread®* for Pediatric Patients**

**How to Mask Unpleasant Taste and Allow Easy Administration**

<table>
<thead>
<tr>
<th><strong>DRUG</strong></th>
<th><strong>Viread® (tenofovir disoproxil fumarate)</strong> is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 2 years of age and older</th>
</tr>
</thead>
</table>
| **NEED** | **More convenient dosage formulation**
  - ease of administration: sprinkled powder for pediatric patients
  - provide highly effective taste masking of a bitter drug |

*VIREAD is a registered trademark of Gilead Sciences, Inc.
©2016 Adare Pharmaceuticals, Inc.*
Viread® - Microencapsulated Particles

Particle morphology after the application of a polymer coating

Coacervated Granule (50x)

Coacervated Granule (90x)

API Granule

Polymer Coating
Viread® Oral Powder: Bioequivalence to Reference IR Tablet

**In vivo** plasma profiles of RLD IR tablet vs. Viread® Oral Powder demonstrated BE

Dissolution profiles from multiple batches demonstrate the reproducibility of the coacervation process.
Viread® - Successful Regulatory Approvals

- FDA approval (2012):
  - NDA for oral powder for the treatment of HIV infection in combination with other antiretroviral agents for children of >=2 years of age

- EMA approval (2012):
  - New granule formulation for the treatment of HIV infection (in combination with other antiretroviral agents) in children ages 2-6 and for children >6 for whom a solid dosage form is not appropriate.

- Commercial presentation:
  - Microcaps® taste-masked oral powder
  - Multi-dose bottle with a calibrated measuring scoop

*VIREAD is a registered trademark of Gilead Sciences, Inc.*
Microcaps® + AdvaTab® Technology
CNS drug ODT case study
AdvaTab® - Robust ODTs with Superior Taste

- Robust: suitable for bottles or blister packs
- High drug loading (up to 500 mg)
- Compress Microcaps® while maintaining absolute taste-masking
- Composed of finely micronized particles rapidly dispersing into a smooth, viscous suspension

Pleasant taste and mouth-feel, ideal for pediatric, geriatric and dysphagic patients
Case Study III: CNS drug ODT
Increase Convenience and Improve Compliance

- Micrographs of Formulation Stages

**API Granule**
(Irregular Shape)

**Microcaps® API**
(Complete & Uniform Taste masking)

**AdvaTab® ODT**
(Pilot Dosage Form)
CNS drug ODT - Bioequivalence to CNS drug IR

**Pivotal Bioequivalence Results**
ODT fasted without water vs. IR, fasted, with water

**Water Effect Results**
(ODT, fasted, with water vs. ODT, fasted, without water)

Pivotal study met FDA guidance for administration with or without water

©2016 Adare Pharmaceuticals, Inc.
Microcaps® formulations exhibited significantly higher scores on both taste and aftertaste.
CNS drug ODT – Patients and Caregivers Prefer ODTs

Subject Preference

Do you prefer the orally disintegrating tablet or the standard tablet?

![Graph showing patient preference between IR and ODT](chart1)

- IR: 26%
- ODT: 74%

Significantly more patients stated that they preferred ODT to IR (p<0.001, N=97)

Companion / Caregiver Preference

Has it been more convenient for the patient to take the orally disintegrating tablet or the standard tablet?

![Graph showing companion/caregiver preference between IR and ODT](chart2)

- IR: 19%
- ODT: 81%

Companion/caregivers concurred with patient’s preference (p<0.001, N=97)

Adherence

Were you more likely to take the ODT tablets as prescribed by your doctor?

![Graph showing adherence between taking ODT and not taking ODT](chart3)

- No, I missed more doses with ODT: 11%
- Yes, I missed fewer doses with ODT: 89%

Significantly more patients reported that they were more adherent on ODT (p<0.001, N=94)

Improves convenience and encourages adherence
CNS drug ODT – Formulation Results

- Rapid dissolution of taste-masked high dose ODT
- Achieved similar mean plasma profiles for ODT with or without water
- Developed four dose proportional tablets with recommended dose of CNS drug ODT matching the dose of CNS drug IR tablets to avoid patient confusion
- Superior acceptability versus reference product
- FDA approved

Product formulation patent (granted in US, JP,...) expiring in 2028
With a Broad Range of Oral Formulation Technologies…

….We Can Help Transform Your Products

• Overcome complex formulation challenges
• Differentiate commercialized products and products in development
  – Improve patient convenience
  – Address specific patient populations
  – Optimize release profiles for new therapeutic uses
• Add valuable IP
Thank You!

Meet us at Booth #11

To learn more, please contact:
holger.neecke@adarepharma.com
luigi.boltri@adarepharma.com