Non-Invasive Drug Delivery: Overview and Emerging Trends PODD 2017

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Non-Invasive Drug Delivery: Overview and Emerging Trends

• Analyze Products/Pipeline and Drug Delivery Technologies
  • Highlight key advancements
    – Approvals, development milestones, trends
• Explore Sales, Deals, Venture Capital
• Conclusions
Non-Invasive Drug Delivery: Overview and Emerging Trends

PRODUCTS AND PIPELINE
Injectables are Taking Over the Pipeline

Route: Marketed vs Pipeline

0 2000 4000 6000 8000 10000 12000

Oral Injectable Topical Ophthalmic Inhalation Transdermal Nasal

Marketed
Pipeline
Drug Delivery Integrated Into Product Development

Marketed Products
- Non-DD: 59%
- DD: 41%

Pipeline Programs
- Non-DD: 69%
- DD: 31%
Innovator Drug Approvals Since 2012

Approvals by Route

- DD vs Non-DD
- Non-DD 55%
- DD 45%
Innovator DD Approvals by Route Since 2012
Innovator Oral DD Approvals Since 2012

- Mature Space
  - Generic companies have capability to develop complex formulations
  - Product development transitioning to CDMO’s
Rapidly Disintegrating Formulations (RDF) Highlights: 2016-2017

- **Monosol Rx**
  - NDA filed for Tadalafil film in US
  - Patent challenges
  - Advancing pipeline
    - Epinephrine, Diazapem, Riluzole films

- **IntelGenx**
  - Film product pipeline progressing
  - Multiple film technology/product patents granted
  - Expanded approvals of film products in additional countries
  - DD technology, product development, marketing deals

- **Neos Therapeutics**
  - Two modified release/ODT/Taste Masking product approvals in US

![RDF Pipeline by Technology](chart.png)
Rapidly Disintegrating Formulations (RDF) Highlights: 2016-2017

• **IX Biopharma**
  – Securing ex-US patents
  – Advancing Rx pipeline

• **CURE Pharmaceuticals**
  – Advancing Rx and OTC pipeline
  – US film patents published

• **BioDelivery Sciences**
  – Marketing deals
  – Expanded approvals of film products in additional countries/indications
  – MonosolRx filed patent infringement lawsuit against BDSI
<table>
<thead>
<tr>
<th>Product</th>
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<th>Route/DF</th>
<th>DD Category/Tech.</th>
<th>Company</th>
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<tbody>
<tr>
<td>ADZENYS XR-ODT (amphetamine)</td>
<td>ADHD</td>
<td>Oral Tablet</td>
<td>Modified Release/ODT/Taste Masking <em>RDIM</em></td>
<td>Neos Therapeutics</td>
</tr>
<tr>
<td>COTEMPLA XR-ODT (methylphenidate)</td>
<td>ADHD</td>
<td>Oral Tablet</td>
<td>Modified Release/ODT/Taste Masking <em>RDIM</em></td>
<td>Neos Therapeutics</td>
</tr>
<tr>
<td>CRESTOR OD Rosuvastatin</td>
<td>Hypercholesterolemia</td>
<td>Oral Tablet</td>
<td>ODT <em>Unspecified</em></td>
<td>Shionogi/Astra Zeneca (Japan)</td>
</tr>
<tr>
<td>DEXILANT SOLUTAB (dexlansoprazole)</td>
<td>Erosive Esophagitis GERD</td>
<td>Oral Tablet</td>
<td>Delayed Release/ODT <em>Solutab</em></td>
<td>Takeda</td>
</tr>
<tr>
<td>LYRICA OD (pregabalin)</td>
<td>Neuropathic Pain Fibromyalgia</td>
<td>Oral Tablet</td>
<td>ODT <em>Unspecified</em></td>
<td>Pfizer/Eisai (Japan)</td>
</tr>
</tbody>
</table>
Oral Macromolecule Highlights: 2016-2017

- **Oramed Pharmaceuticals**
  - End of Phase 2 meeting with FDA for Oral Insulin
  - GLP-1 analog program completed Phase 1
  - Granted patents US, EU, Japan

- **Chiasma**
  - Mycapssa (octreotide) Phase 3 design with FDA 8/2017
    - First Phase 3 subject randomized 9/2017
  - Mycapssa (octreotide) CRL 4/2016

- **Enteris BioPharma**
  - Cara CR845 oral program completed Phase 2
  - Advancing Ovarest (leuprolide) Phase 2 and Tobrate (tobramycin) Phase 1 programs
  - Technology deals with Ferring, KeyBioscience, Sanofi
Oral Macromolecule Highlights: 2016-2017

- **3P Biotechnologies, Inc./University of Louisville**
  - Exclusively licensed Calix milk exosome technology to Puretech

- **Rani Therapeutics**
  - “Robotic” capsule delivers macromolecules into the intestinal wall
  - Collaboration deal with MedImmune
  - Completed latest round of financing (total investment $70 million)
Ophthalmic Highlights: 2016-2017

- **Clearside Biomedical** (hollow microneedle technology delivers to suprachoroidal space)
  - Completed Zuprata Phase 3 enrollment
  - US patent allowances (9 in total)
  - IPO in 2016

- **Arie Pharmaceuticals**
  - FDA Advisory date set for Rhopressa (netarsudil) Topical Solution
  - Positive Phase 3 results for Roclatan (netarsudil, latanaprost) Topical Solution
  - Deal with Envisia Therapeutics for PRINT implant technology
  - Deal with DSM for DSM’s polymer delivery technology
  - Successful public offering financing rounds

- **Eyegate**
  - Initiated Phase 2b study for EGP-437 iontophoretic delivery of dexamethasone
  - License deal with Valeant for EGP-437
  - Positive first in human data for ocular bandage program
  - Successful financing rounds
Ophthalmic Highlights: 2016-2017

- **Allergan**
  - Launch of RESTASIS MULTIDOSE which utilizes a patented, unidirectional valve and air filter technology that eliminates the need for a preservative.

- **Nicox**
  - Zerviate (cetirizine) ophthalmic solution approved by FDA
  - Zerviate license deal with Eyevance
  - Licensed pSivida implant technology
  - Valeant responds to Vyzulta (latanoprostene) ophthalmic solution CRL
    - cGMP issues at CMO

- **Envisia Therapeutics (spun out of Liquidia)**
  - Positive interim Phase 2 data for ENV515 (travoprost XR)
  - Deal with Aerie
  - Successful financing rounds

- **GrayBug Vision**
  - Initiated Phase 1/2 trial for GB-102 (sunitinib) in AMD
    - Depot formulation of drug encapsulated within bioabsorbable microparticles
    - Twice-yearly IVT injection (not exactly non-invasive but notable advancement)
Ophthalmic Highlights: 2016-2017

- Topical most common technology category
- Unmet needs
  - Back of the eye delivery
  - Convenient administration
    - Easy to use delivery application device
    - Reduce frequency

Products/Pipeline by Technology Category

- Topical 86%
- Delivery Devices/Dispensers 8%
- Implants/Rods 5%
- Photodynamic 1%
- Iontophoresis <1%
Inhalation Highlights: 2016-2017

• Vectura Group
  – Acquired SkyePharma
  – Approval/Launch of Ventavis delivery with FOX® based Breelib® nebulizer
  – Partnering with Pulmatrix for development of PUR0200
  – Hikma generic Advair Diskus (VR315) received CRL
  – Multiple Deals (Mundipharma, Hikma, Sandoz, Dynavax, Propeller Health)
  – Multiple pipeline advancements

• Orion
  – Planning for salmeterol-fluticasone EasyHaler marketing authorization
Inhalation Highlights: 2016-2017

• **Aptar Pharma**
  – Unveils Integrated Connected Inhalers platform
    • Devices are connected to the Propeller Health mobile application and services

• **Adherium** (adherence monitoring technology)
  – Release of SmartTurbo Model 4 for AstraZeneca’s Turbuhaler
  – US 510(K) Clearance of SmartTouch for Symbicort® inhaler monitoring device

• **Pearl Therapeutics** (Astra Zeneca Group)
  – Bevespi Aerosphere (glycopyrrolate, formoterol) utilizing Pearls’ HFA formulation approved in US

• **Aradigm**
  – Linhaliq (ciprofloxacin) US NDA submitted/accepted
Innovator Inhalation Approvals Since 2012

- Approvals With Same Platform
  - **Novartis Breezehaler** (DPI): Seebri (2012), Ultibro (2013), other prior to 2012
  - **Almirall Genuair** (DPI): Eklira (2012), Brimica/Duaklir (2014), others prior to 2012
  - **BI Respimat** (Nebulizer): Striverdi (2013), Stiolta (2015), others prior to 2012
  - **Pari eFlow** (Nebulizer): Quinsair (2015), Vantobra (2015), other prior to 2012

- Inhaled combination products difficult to develop as a generic
Topical Highlights: 2016-2017

- **Novan** (controlled release topical gel/cream, NO gas in biopolymer)
  - Phase 3 for Acne Vulgaris product SB204
    - FDA guidance meeting 9/2017
  - License deal with Sato for SB204 in Japan
  - Advancing pipeline SB208 antifungal (Phase 2), SB206 genital warts (Phase 2) and SB414 anti-inflammatory (preclin)

- **Foamix**
  - Advancing topical minocycline foam programs
    - Completed FMX101 Phase 3 enrollment for Acne
    - Initiated FMX103 Phase 3 trial for Rosacea

- **Leo Pharma**
  - Acquired Astellas dermatology business
  - Topical products approvals, deals...
  - Strategic deals in non-topical, dermatology programs
  - Investment in Novopyxsis
    - Novel device for topical delivery. Potential for macromolecule delivery to deep skin.
Transdermal Highlights: 2016-2017

• Limited NDA approvals since 2012
• Apricus Biosciences
  – Re-submitted US NDA for Vitaros (alprostadil) drug-device combination
    • Vitaros utilizes NexACT transdermal enhancer in conjunction with disposable applicator
  – Multiple ex-US approvals/launches of Vitaros
  – Sold ex-US assets of Vitaros to Ferring for $13 million ($11.5 upfront)
• BiPhasix Technology (topical/transdermal macromolecule delivery)
  – Pivot Pharmaceuticals licenses for development of cannabinoid products.
  – Technology and products (topical interferon alpha 2b) acquired by Altum
  – Helix Biopharma sold technology to Xisle Pharma Ventures
Transdermal Highlights: 2016-2017

• **Aequus Pharmaceuticals**
  - Success POC clinical trials of AQS1303 (pyridoxine, doxylamine) patch
  - Advancing AQS1301 once-weekly transdermal aripiprazole patch
    • Suitable for 505(b)(2) pathway
    • Successful Phase 1 POC
    • Filed/granted international patents
  - Licensed AQS1304 cannabinoid patch from Transdermal Research Pharma Lab

• **Illustris Pharmaceuticals**
  - Novel transdermal/transmucosal delivery technology which employs peptide/polysaccharide decoys to enable drug absorption
    • Deliver molecules up to 160 KD
Microneedle Highlights: 2016-2017

• Many programs have been discontinued or placed on hold
• Zosano Pharma
  – Positive M207 (zolmitriptan) Phase 2 migraine results
  – M207 end of Phase 2 meeting with FDA
• Nanopass Technologies
  – Positive Phase 2 cancer data for Immune Design’s CMB305 prime-boost immuno-oncology agent in conjunction with atezolizumab
  – Deal with IDRI to develop intradermal rvRNA-based Zika virus vaccine
  – Positive ID vaccination in elderly data presented by Crucell
  – Strategic investment by West
• 3M
  – hMTS technology collaboration with Panacea Pharmaceuticals for cancer vaccine
  – Radius presented abaloparatide osteoporosis microneedle patch results
Microneedle Highlights: 2016-2017

• **Nemaura**
  – Memspatch IMD compared favourably against a commonly-use marketed Pen Injector
  – Completed preclinical immunogenicity studies for Tdap triple vaccine
  – Secured funding

• **Micron Biomedical**
  – Phase 1 trial showed vaccination by microneedle patch was as safe and at least as immunogenic as vaccination with standard needle and syringe
  – Measles collaboration with CDC and Georgia Tech

• **Microdermics**
  – Development collaboration with Vetter
  – Successful funding to scale up technology

• **SkinJect**
  – Licensed dissolvable microneedle patch technology from University of Pittsburgh to deliver chemotherapeutics
Nasal Highlights: 2016-2017

• **Aegis Therapeutics**
  • Phase 1 trial of Opiant’s Intravail enabled OPNT002 (naltrexone)
  • Opiant licenses Intravail technology
  • Positive Phase 2 data for Reddy’s/Promius DFN02 (sumatriptan)
  • Patents awarded for migraine and octreotide
  • Dauntless reported positive Phase 1 data for intranasal octreotide DP1038
  • Developed rapid onset hydropromormone formulation

• **Optinose**
  • FDA approval of XHANCE (fluticasone)
  • Approval/launch ONZETRA Xsail (sumatriptan)
  • Successful funding
  • Evaluating nose to brain delivery with grant from Norwegian government

• **Mundipharma**
  – Nyxoid (naloxone) positive opinion in EU
Needle Free Injector Highlights: 2016-2017

**PharmaJet**
- FDA Approval of Sequiris’s AFLURIA QUADRIVALENT (Influenza Vaccine)
- Vaccibody collaboration on HPV vaccine
- WHO collaboration in polio
- Partnership with Serum Institute to Launch Needle-Free MMR Vaccine

**Inovio**
- Acquired Bioject’s technology assets

**Antares**
- Sold Zomajet needle free system to Ferring

**Crossject**
- Receives authorization to conduct Zeneo (midazolam) BE Study

**Glide Pharma**
- Assets sold to Enesi Pharma Limited
- SDI octreotide (100 mcg) achieved bioequivalence to Sandostatin liquid
- Completed pre-clinical proof-of-concept study for SDI exenatide
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DRUG DELIVERY TECHNOLOGIES
Overview: Drug Delivery Technologies

Technology Count by Technology Category

As published in Drug Development and Delivery Global Formulation Report September 2017
Overview: Drug Delivery Technologies

Technology Count by Therapeutic Application

- Cancer
- Endocrine
- Infections
- CNS
- Inflammation/Immune
- Pain Management
- Cardiovascular
- Respiratory
- Musculoskeletal
- Eye Diseases
- Gastrointestinal
- All Other
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SALES, DEALS, VENTURE CAPITAL
Top 10 Non-Injectable DD Sales 2016

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<th>DD Category/ Technology</th>
<th>Company</th>
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<tbody>
<tr>
<td>Harvoni (sofosbuvir, ledipasvir)</td>
<td>Hepatitis C</td>
<td>9081</td>
<td>Oral Tablet</td>
<td>Amorphous Dispersion Spray Drying</td>
<td>Gilead</td>
</tr>
<tr>
<td>Advair (salmeterol, fluticasone)</td>
<td>Asthma COPD</td>
<td>4727</td>
<td>Inhalation Powder, HFA Aerosol</td>
<td>DPI, MDI Diskus, Multiple¹</td>
<td>GSK</td>
</tr>
<tr>
<td>Tecfidera (dimethyl fumarate)</td>
<td>Multiple Sclerosis</td>
<td>3968</td>
<td>Oral Capsule</td>
<td>Enteric/Delayed Release Unspecified</td>
<td>Biogen</td>
</tr>
<tr>
<td>Spiriva (tiotropium bromide)</td>
<td>Asthma COPD</td>
<td>3315</td>
<td>Inhalation Powder, Solution</td>
<td>DPI, Nebulizer Handihaler, Respimat</td>
<td>Boehringer Ingelheim</td>
</tr>
<tr>
<td>Symbicort (budesonide, formoterol)</td>
<td>Asthma COPD</td>
<td>2989</td>
<td>Inhalation Powder, Suspension</td>
<td>DPI, MDI TurbuHaler, Multiple²</td>
<td>AstraZeneca</td>
</tr>
</tbody>
</table>

1: GSK HFA, GSK Dose Counter, Aptar pMDI  2:Aptar pMDI, AZ HFA, AZ Dose Counter, Adherium SmartInhaler
## Top 10 Non-Injectable DD Sales 2016

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<tr>
<td>Restasis (cyclosporine)</td>
<td>Dry Eye</td>
<td>2985</td>
<td>Ophthalmic Emulsion</td>
<td>Topical, Device/Dispenser <em>Aptar Squeeze Dispenser</em></td>
<td>Allergan</td>
</tr>
<tr>
<td>XTANDI (enzalutamide)</td>
<td>Cancer</td>
<td>2327</td>
<td>Oral Softgel</td>
<td>Oral Lipid &amp; SEDDS <em>Unspecified</em></td>
<td>Astellas</td>
</tr>
<tr>
<td>Janumet/Janumet XR</td>
<td>Diabetes</td>
<td>2200</td>
<td>Oral Tablet</td>
<td>Matrix MR/Gastroretentive <em>Depomed Acuform</em></td>
<td>Merck</td>
</tr>
<tr>
<td>Nexium (esomeprazole)</td>
<td>GERD</td>
<td>2032</td>
<td>Oral Capsule, Tablet, Suspension</td>
<td>Delayed Release <em>Unspecified</em></td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>Vyvanse (lisdexamfetamine dimesylate)</td>
<td>ADHD</td>
<td>2014</td>
<td>Oral Capsule</td>
<td>Abuse Resistant <em>CarrierWave</em></td>
<td>Shire</td>
</tr>
</tbody>
</table>
Drug Delivery Related Deals Since 2012

Drug Delivery Related Deals by Technology Category

Drug Delivery Related Deals by Year

Includes product/technology deals and acquisitions in DD
Drug Delivery Companies Formed Since 2012

Companies by Technology Category

- Injection: 120
- Skin: 20
- Oral: 30
- Ophthalmic: 40
- Drug Delivery: 50
- Transmucosal: 10
- Inhalation: 20
- Medical Devices: 30
- Other: 10
Drug Delivery Venture Capital Funding Since 2012

Venture Capital Funding by DD Category

INJECTION: 38%
INHALATION: 5%
MEDICAL DEVICES: 6%
TRANSMUCOSAL: 7%
OTHER CATEGORIES: 9%
OPHTHALMIC: 8%
SKIN: 11%
ORAL: 16%
OTHER CATEGORIES: 9%
CONCLUSIONS

• Drug Delivery Applied Across Products/Pipeline
  – ~40% marketed products apply DD technology
• Injectables becoming majority of pipeline
  – Large focus on injection based devices/biologics
• CDMO’s Becoming Centers for Technology/Product Development
• Drug Delivery and Compliance Devices
  – Continued development of devices across routes not just injection
• Needs Based Approach to DD Technology/Product Development
• Digital Medicine
  – Rapidly advancing in all areas using smart phone based apps
CONCLUSIONS

• Oral
  – Space has certainly matured.

• Inhalation
  – Leverage device platforms across multiple products
  – Connectivity with compliance/digital health platforms

• Nasal
  – Applicable to fast acting (i.e. migraine) and macromolecule delivery

• Ophthalmic
  – Unmet needs in back of the eye delivery

• Transdermal/Topical
  – Very few NDA transdermal approvals in last 5 years
  – Convenient administration
  – Alternative macromolecule delivery