

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

Kurt R. Sedo
Vice President, Operations
PharmaCircle LLC
Encinitas, CA

Non-Invasive Drug Delivery: Overview and Emerging Trends

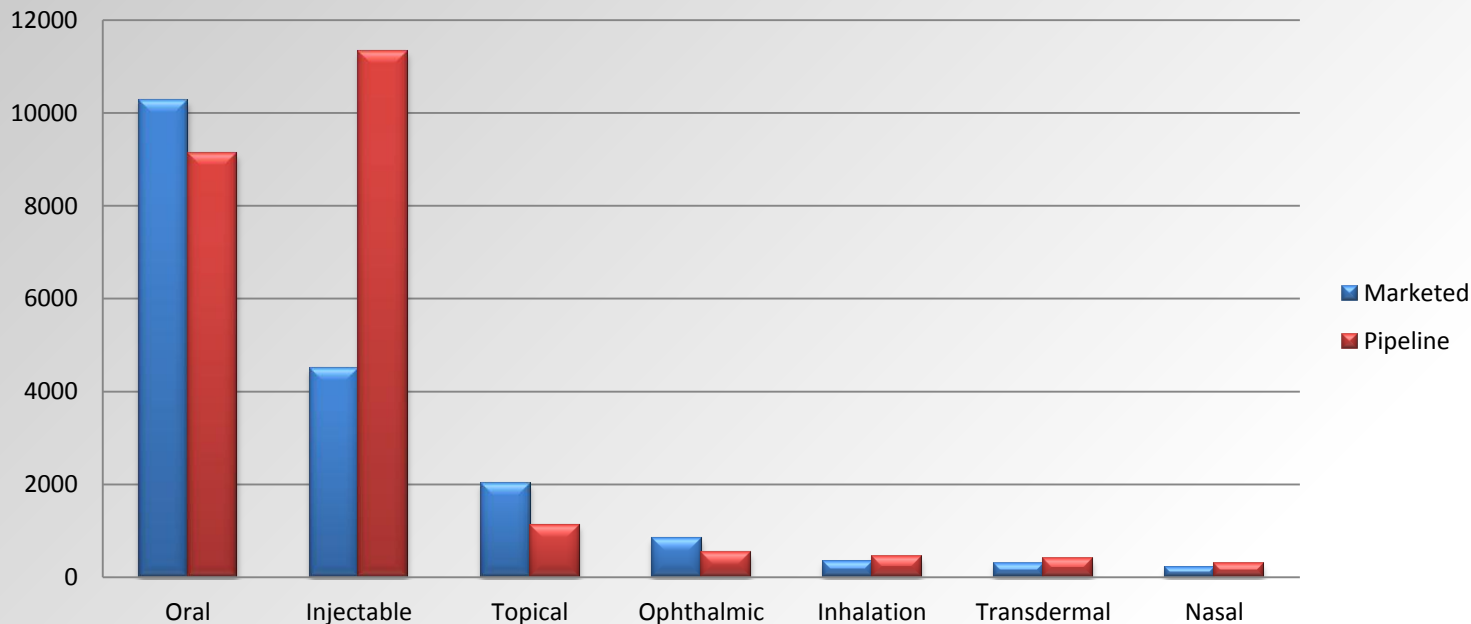
- Analyze Products/Pipeline and Drug Delivery Technologies
 - Highlight key advancements
 - Approvals, development milestones, trends
- Explore Sales, Deals, Venture Capital
- Conclusions

Non-Invasive Drug Delivery: Overview and Emerging Trends

PRODUCTS AND PIPELINE

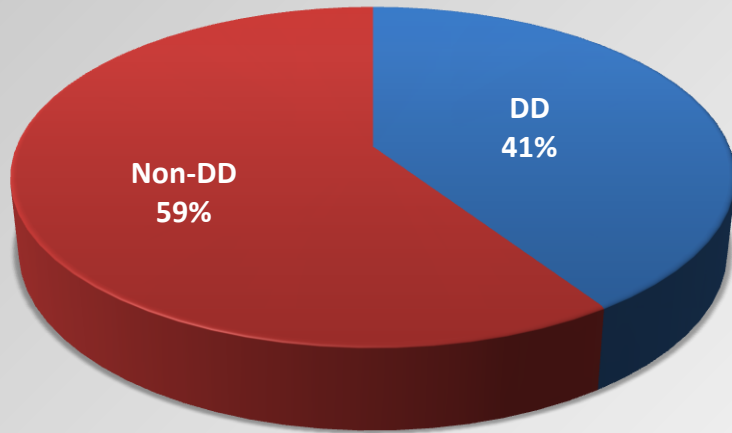
Injectables are Taking Over the Pipeline

Route: Marketed vs Pipeline

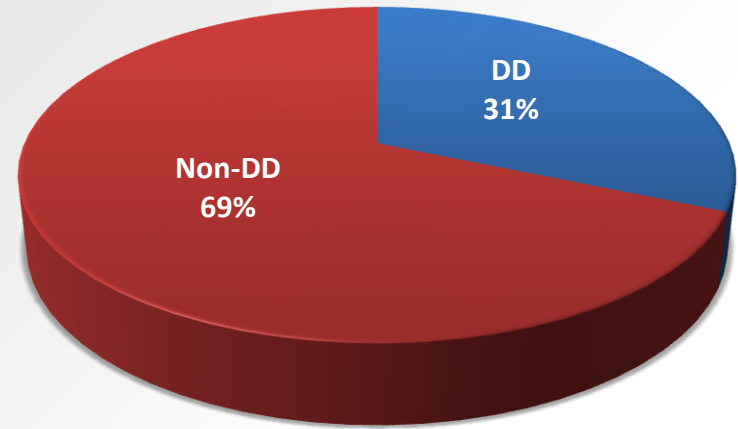


Drug Delivery Integrated Into Product Development

Marketed Products

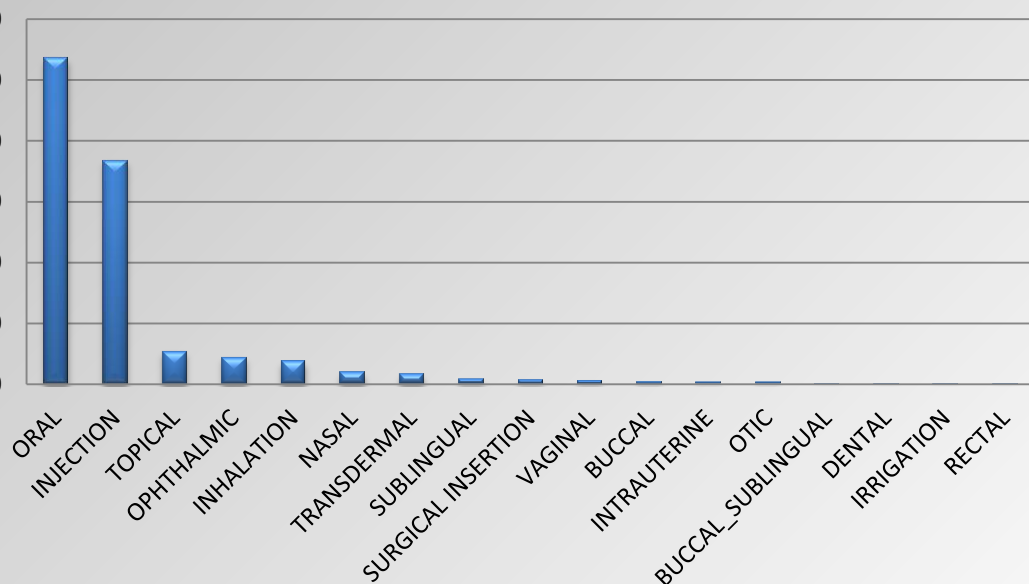


Pipeline Programs

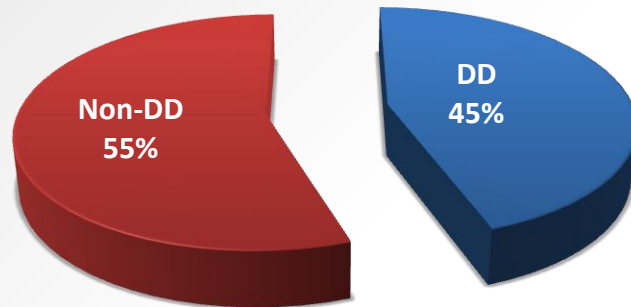


Innovator Drug Approvals Since 2012

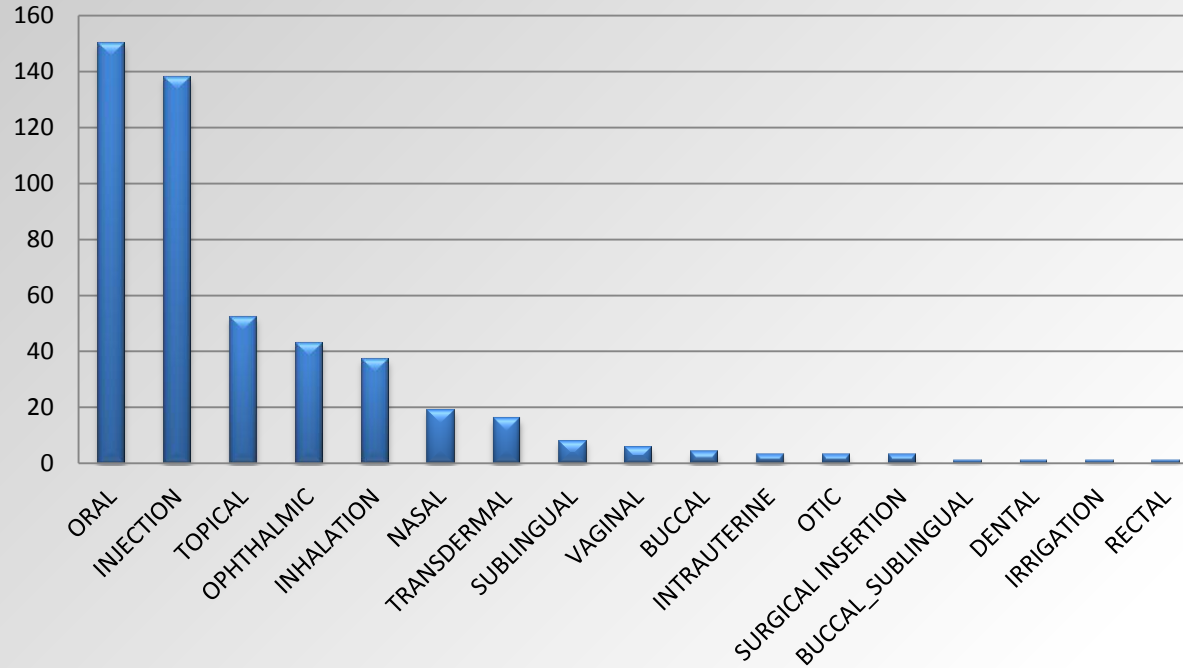
Approvals by Route



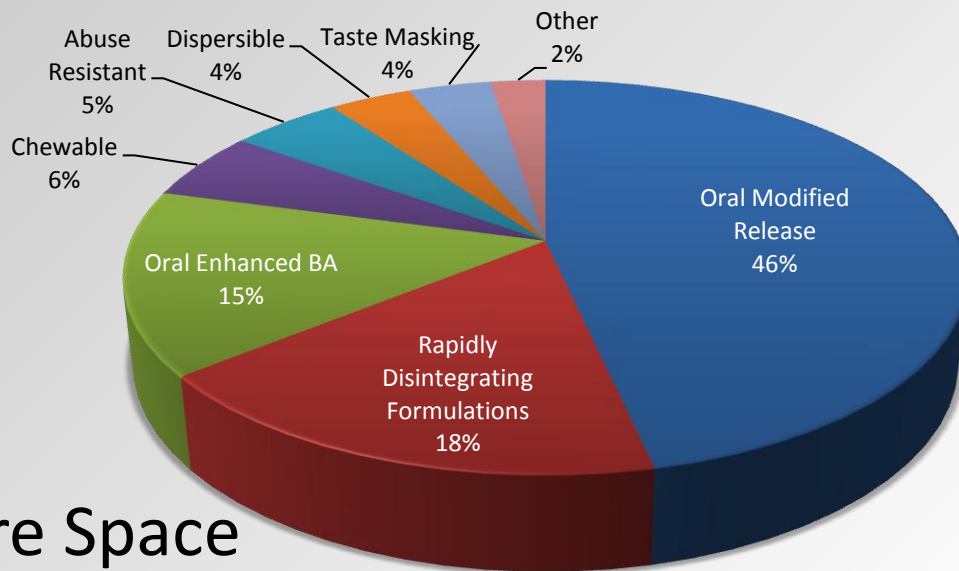
DD vs Non-DD



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, Diazepam, Riluzole films

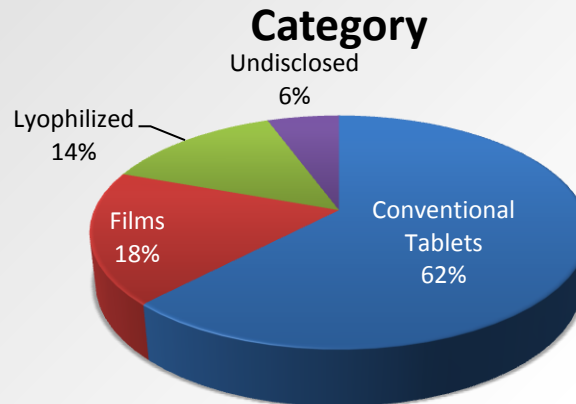
- **IntelGenx**

- 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



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

RDF: Key Approvals 2016-2017

Product	Indication	Route/DF	DD Category/Tech.	Company
ADZENYS XR-ODT (amphetamine)	ADHD	Oral Tablet	Modified Release/ODT/Taste Masking RDIM	Neos Therapeutics
COTEMPLA XR-ODT (methylphenidate)	ADHD	Oral Tablet	Modified Release/ODT/Taste Masking RDIM	Neos Therapeutics
CRESTOR OD Rosuvastatin	Hypercholesterolemia	Oral Tablet	ODT Unspecified	Shionogi/Astra Zeneca (Japan)
DEXILANT SOLUTAB (dexlansoprazole)	Erosive Esophagitis GERD	Oral Tablet	Delayed Release/ODT Solutab	Takeda
LYRICA OD (pregabalin)	Neuropathic Pain Fibromyalgia	Oral Tablet	ODT Unspecified	Pfizer/Eisai (Japan)

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

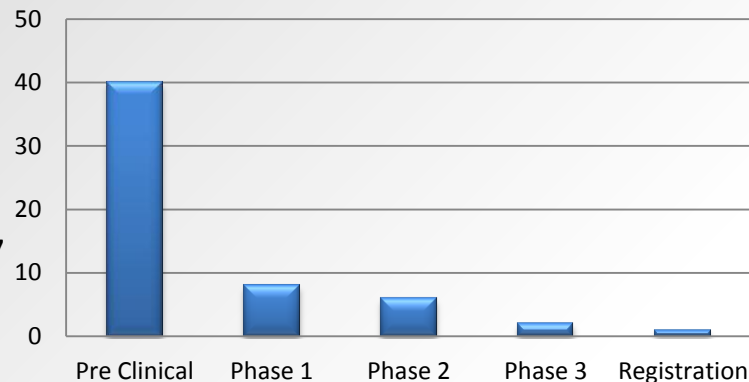
- **Chiasma**

- 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 by Phase



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

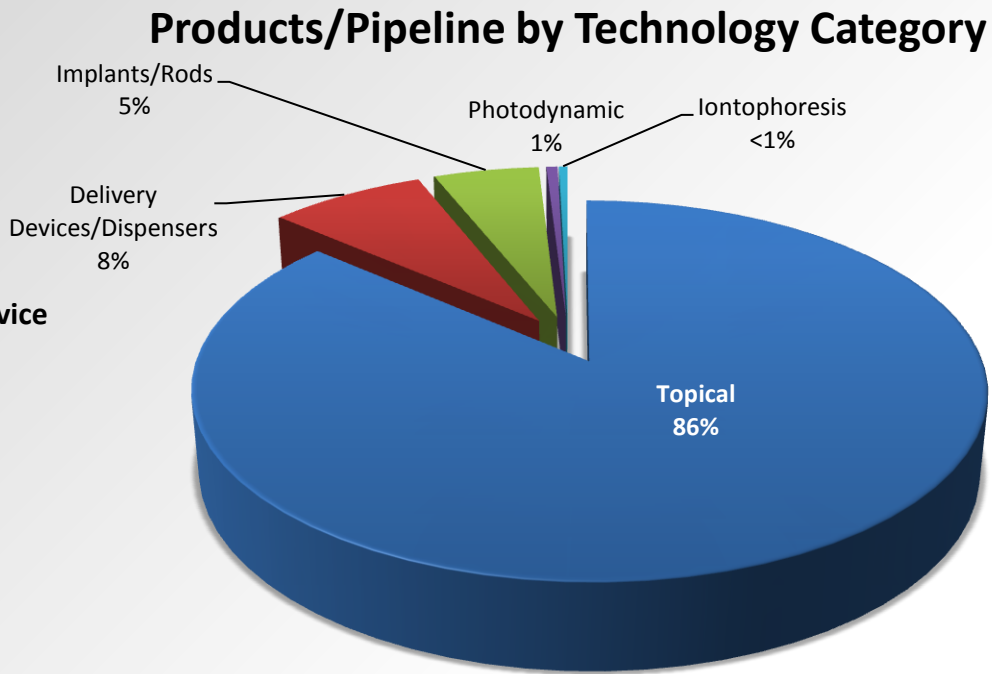
- **Clearside Biomedical** (hollow microneedle technology delivers to suprachoroidal space)
 - Completed Zuprata Phase 3 enrollment
 - US patent allowances (9 in total)
 - IPO in 2016
- **Arie Pharmaceuticals**
 - FDA Advisory date set for Rhopressa (netarsudil) Topical Solution
 - Positive Phase 3 results 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



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**

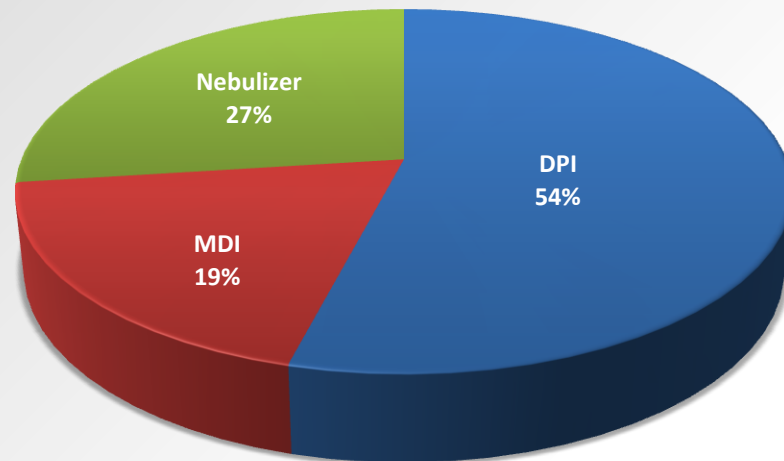
- Planning for salmeterol-fluticasone EasyHaler marketing authorization

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
 - **GSK Ellipta** (DPI): **Anoro** (2013), **Breo** (2013), **Arnuity** (2014), **Incruse** (2014), **Trelegy** (2017)
 - **Novartis Breezhaler** (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
 - **Teva RespiClick/Spiromax** (DPI): **Biresp** (2014), **ProAir** (2015), **AirDuo** (2016), **ArmonAir** (2017)
- Inhaled combination products difficult to develop as a generic



**Inhalation Approvals by
Technology Category**

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 Phase3 trial for Rosacea
- **Leo Pharma**
 - Acquired Astellas dermatology business
 - Topical products approvals, deals...
 - Strategic deals in non-topical, dermatology programs
 - Investment in Novopyxis
 - 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
 - Suspended development of pTH programs Daily B104/Weekly B206 and D107 glucagon.
- **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 hydrophormone 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**

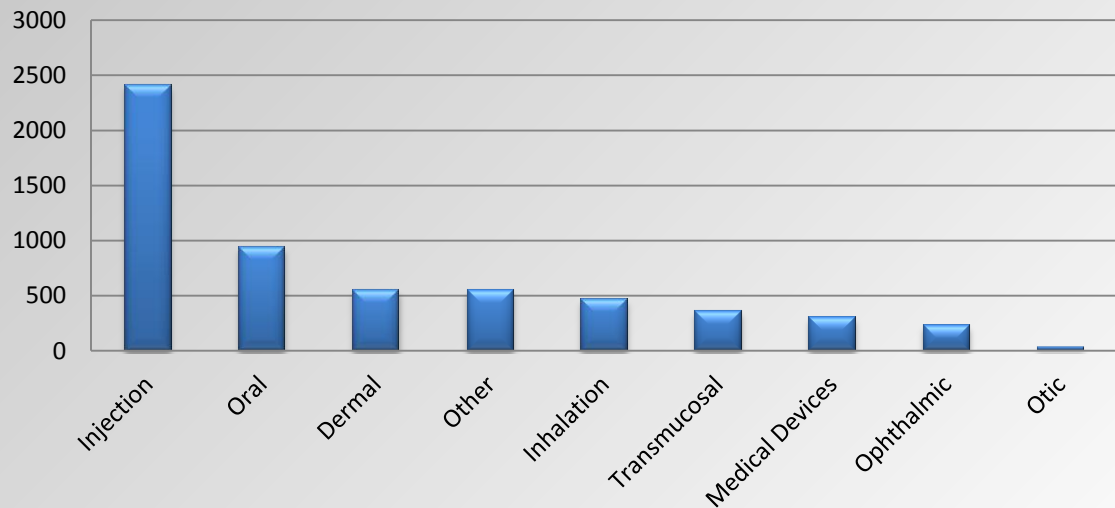
- Assets sold to Enesi Pharma Limited
- SDI octreotide (100 mcg) achieved bioequivalence to Sandostatin liquid
- Completed pre-clinical proof-of-concept study for SDI exenatide

Non-Invasive Drug Delivery: Overview and Emerging Trends

DRUG DELIVERY TECHNOLOGIES

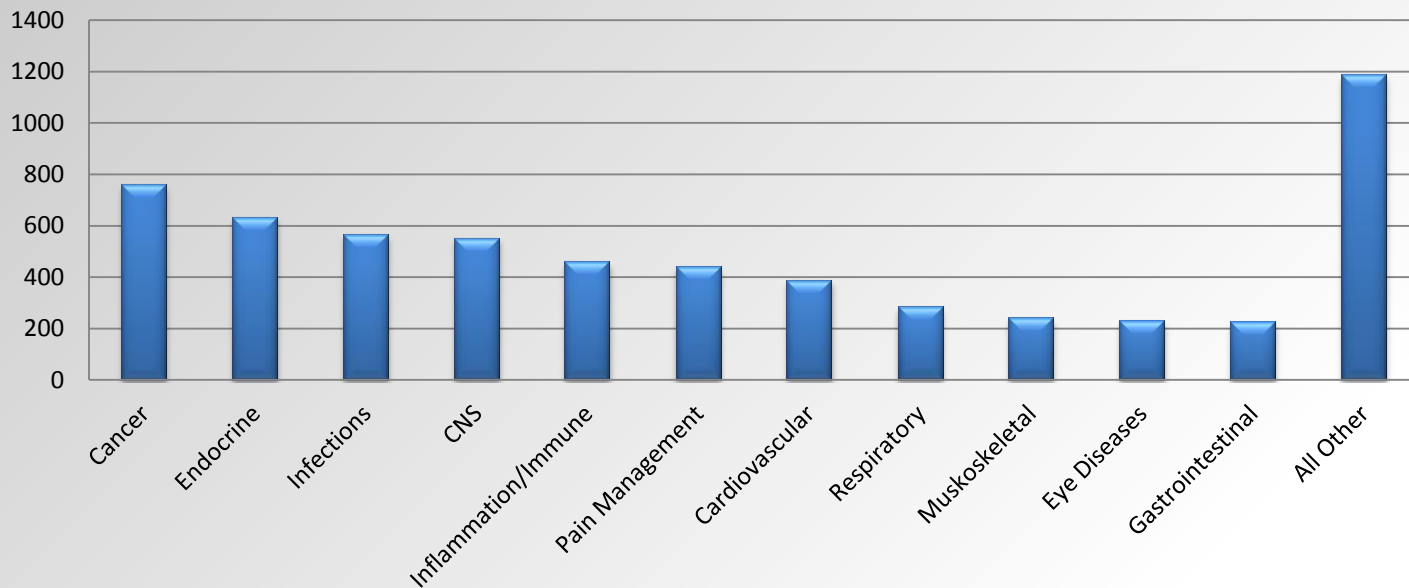
Overview: Drug Delivery Technologies

Technology Count by Technology Category



Overview: Drug Delivery Technologies

Technology Count by Therapeutic Application



Non-Invasive Drug Delivery: Overview and Emerging Trends

SALES, DEALS, VENTURE CAPITAL

Top 10 Non-Injectable DD Sales 2016

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

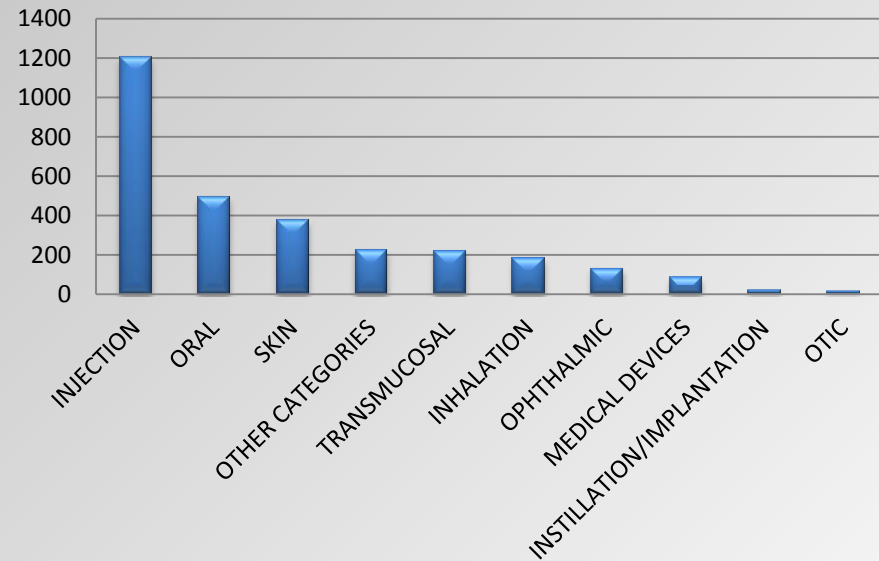
1: GSK HFA, GSK Dose Counter, Aptar pMDI 2:Aptar pMDI, AZ HFA, AZ Dose Counter, Adherium SmartInhaler

Top 10 Non-Injectable DD Sales 2016

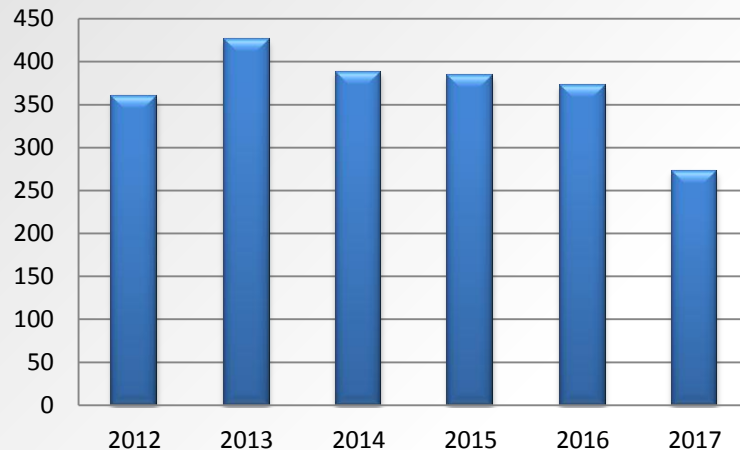
Product	Indication	Sales (USD mil)	Route/ DF	DD Category/Tech.	Company
Restasis (cyclosporine)	Dry Eye	2985	Ophthalmic Emulsion	Topical , Device/Dispenser <i>Aptar Squeeze Dispenser</i>	Allergan
XTANDI (enzalutamide)	Cancer	2327	Oral Softgel	Oral Lipid & SEDDS <i>Unspecified</i>	Astellas
Janumet/Janumet XR (sitagliptin, metformin)	Diabetes	2200	Oral Tablet	Matrix MR/Gastroretentive <i>Depomed Acuform</i>	Merck
Nexium (esomeprazole)	GERD	2032	Oral Capsule, Tablet, Suspension	Delayed Release <i>Unspecified</i>	AstraZeneca
Vyvanse (lisdexamfetamine dimesylate)	ADHD	2014	Oral Capsule	Abuse Resistant <i>CarrierWave</i>	Shire

Drug Delivery Related Deals Since 2012

Drug Delivery Related Deals by Technology Category



Drug Delivery Related Deals by Year

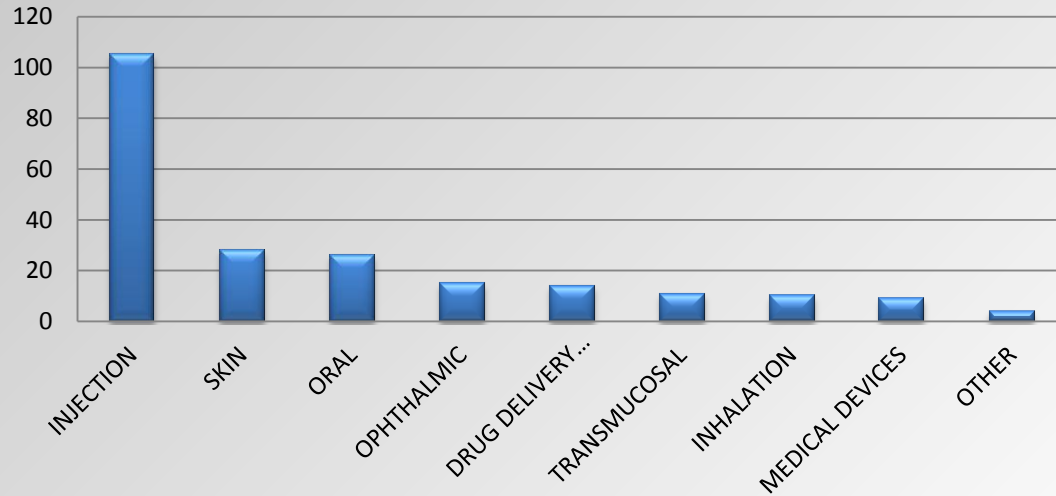


Includes product/technology deals and acquisitions in DD



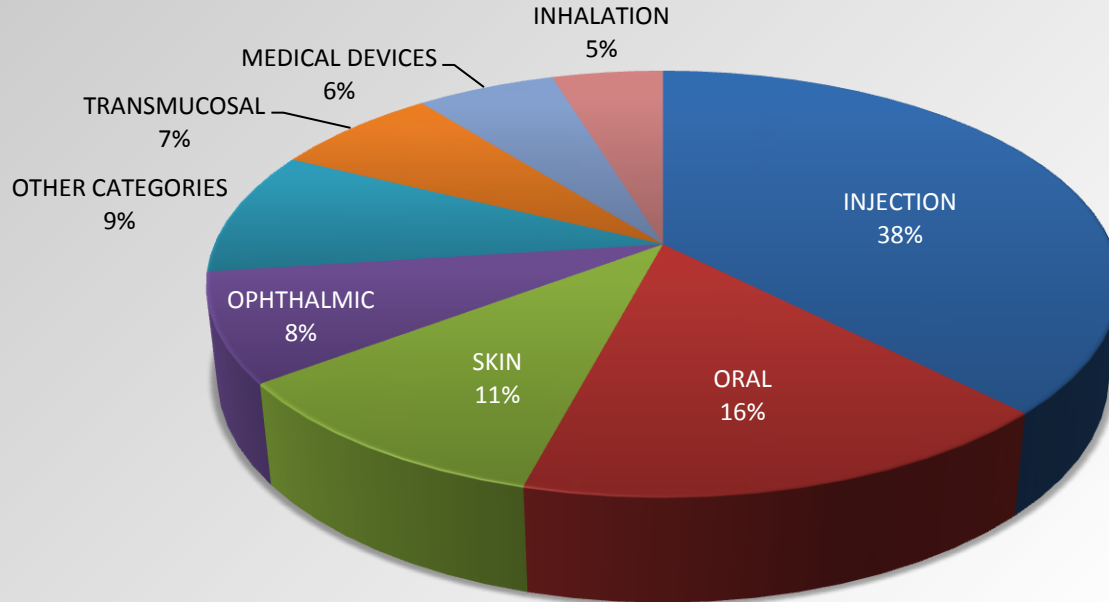
Drug Delivery Companies Formed Since 2012

Companies by Technology Category



Drug Delivery Venture Capital Funding Since 2012

Venture Capital Funding by DD Category



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