



2018

Global Drug Delivery & Formulation

R E P O R T

Three of a Four-Part Series

Part 1: A Global Review of 2018 Product Approvals

Part 2: Notable Product Drug Delivery and Formulation Approvals of 2018

Part 3: Notable Drug Delivery and Formulation Transactions and Technologies of 2018

Part 4: The Drug Delivery and Formulation Pipeline

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Introduction

It feels as though 2018 was a subdued year in terms of notable drug delivery product and technology deals. There were some of the typical deals as exemplified by Halozyme adding on to their partnership with Roche on the same terms as the past few years. Where things deviated from the usual was in the area of gene and cell therapy. The objective with many gene and cell therapy technologies parallels that of more traditional small molecule technologies, targeted delivery with customized pharmacodynamic properties. The Voyager Therapeutics agreement with AbbVie, for example, is intended to harness the Voyager technology to selectively target and deliver AbbVie's antibody transgenes across the blood brain barrier. The modern drug delivery and formulation toolbox needs to make room for these new gene and cell therapy technologies.

Quantitatively, Pharma transactions as a whole rose a respectable 6% in 2018 with a bit of a shift to Technology deals, up 19%, while Product Deals were up a more modest 5%.

In terms of drug delivery and formulation technologies, 2018 saw another 500 or so Active Technologies added to the toolbox, bringing the total to a little over 5,300. The majority of these technologies are still applicable to Injection-related applications, although its share dropped a point in 2018. The difference was made up by Medical Devices and the category of All Other as described later in this report.

This short overview of drug delivery and formulation transactions includes some of the numbers that color the trends of 2018 along with some thoughts on Notable Transactions and Technologies.

Special Thanks to Esay Okutgen, PhD, Director, Drug Delivery, PharmaCircle LLC for technical input.

Overall Transactions Were Up a Modest 5% in 2018

Table 1. Pharma Transactions 2018 and 2017 by Business Category

Business Category	2018	2017	Change (Y/Y)
Drug Delivery	415	408	2%
Company Acquisitions	4	12	
DD Technology Deals	169	136	24%
Discovery Technology Deals	5	13	
Joint Venture Deal	5	2	
Option Agreement	11	5	
Product Acquisitions	13	14	
Product Deals	207	225	-8%
Technology Acquisitions	1	1	
Generics	49	20	145%
Company Acquisitions	6	8	
Product Acquisitions	11	4	
Product Deals	32	8	300%
Pharma Services	873	852	2%
Company Acquisitions	137	150	-9%
DD Technology Deals	1	0	
Discovery Technology Deals	13	14	
Joint Venture Deal	1	2	
Pharma Services Deals	720	684	5%
Product Deals	0	2	
Technology Acquisitions	1	0	
PharmaBio	1194	1118	7%
Company Acquisitions	74	123	-40%
DD Technology Deals	8	2	
Discovery Technology Deals	279	201	39%
Joint Venture Deal	12	13	
Option Agreement	34	26	31%
Product Acquisitions	33	41	-20%
Product Deals	751	707	6%
Technology Acquisitions	3	5	
Other	17	5	
Total	2548	2403	6%

Source: PharmaCircle Strategic Deals Analyzer Module

Table Notes:

1. PharmaBio figures include Specialty Pharma transactions.
2. Transactions do not include Amendment or Termination Agreements.
3. Other includes Biosimilars.
4. Drug Delivery transactions are those where at least one element (technology, product) or one party to the transaction involves a drug delivery labeled asset.
5. Percentages are not provided where the underlying numbers are low.

- There was an overall 6% increase in transactions between 2017 and 2018. PharmaBio Company Acquisitions dropped (-40%). Does this suggest companies, been picked over or are the premiums too high?
- Drug Delivery transactions saw a perhaps significant shift from product related deals (-8%) to technology deals (+24%). Discovery Technology deals increased (+39%) perhaps reflecting an interest in doing more internal pipeline development.
- While there is only limited public data, Generics Product Deals were up a robust 300%. Pharma Service deals were up 5% and represented a bit more than a quarter of all transactions.

Product Related Deals Accounted for Almost Half of All Pharma Transactions in 2018

Table 2. Pharma Transactions 2018 and 2017 by Deal Type

Transaction Type	2018	2017	Change (Y/Y)	Share of Total (2018)
Pharma Services Deals	720	684	5%	28%
Product Deals	1,061	1,006	5%	42%
Product Acquisitions	58	60	-3%	2%
Product Deals	1,003	946	6%	39%
Technology Deals	480	372	29%	19%
DD Technology Deals	178	138	29%	7%
Discovery Technology Deals	297	228	30%	12%
Technology Acquisitions	5	6		
All Other	287	341	-16%	11%
Total	2,548	2,403	6%	6%

Source: PharmaCircle Strategic Deals Analyzer Module

Table Notes:

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3. Drug Delivery transactions are those where at least one element (technology, product) or one party to the transaction involves a drug delivery labeled asset.
4. Percentages are not provided where the underlying numbers are low.

- Product deals accounted for a little more than two fifths of all Pharma related transactions in 2018, an increase of 5% over 2017.
- Technology deals in 2018 accounted for a fifth of all transactions with a sharp 29% increase over 2017.
- Discovery Technology deals accounted for 62% of Technology deals, up a solid 29%.
- Pharma Service deals remain an important segment for both established and emerging PharmaBio companies.



Notable Drug Delivery and Formulation Related Technology Transactions of 2018

Technology: Open-Inhale-Close, Lever Operated (LOMI) DPI

Indication: Asthma, COPD

Delivery Route: Inhalation

Licensors/Licensee: Vectura Group/Hikma

Deal Value/Upfront: \$95 million/\$15 million

Royalty: Mid-teens

Deal Summary: An agreement to pursue generics of GSK's Ellipta franchise. Vectura to develop and deliver prototypes to Hikma for development and commercialization.

Notable: After dodging Advair generics for what seems a decade, GSK is facing the prospect of aggressive generic development to its Ellipta platform from Vectura, a previous formulation technology partner.



Technology: GalXC platform

Indication(s): Neurodegenerative, Pain, Cardiometabolic

Delivery Route: Injection

Licensors/Licensee: Dicerna/Eli Lilly

Deal Value/Upfront: >\$550 million/\$200 million (License fee and equity)

Royalty: Mid-single to low-double digits

Deal Summary: The deal covers up to ten targets with little information provided beyond selected financial terms and general targets. Terms include up to \$350 million per target in milestones.

Notable: The deal involves RNAi therapeutics using Dicerna's GalXC liver targeted platform that attaches sugars to Dicer substrate short-interfering RNA (DsiRNA-EX) molecules to deliver and silence specific gene targets within the cells.



Technology: Afibromer technology

Indication: Type-1 Diabetes

Delivery Route: Implant

Licensors/Licensee: Sigilon/Eli Lilly

Deal Value/Upfront: \$473 million/\$63 million

Deal Summary: Sigilon will be responsible for development activities and costs related to the collaboration until submission of an investigational new drug application (IND). Post IND Lilly will be responsible for all clinical development and commercialization activities and costs.

Notable: The holy grail of Type-1 Diabetes is being pursued using the cell encapsulation of islet cells with Sigilon's Afibromer polymer, an implantable biomaterial that is claimed to minimize immune response.



Technology: Calix Exosomes

Indication: Undisclosed

Delivery Route: Oral

Licensors/Licensee: PureTech Health/Roche

Deal Value/Upfront: >\$1 billion \$36 million

Deal Summary: Under the terms of the agreement, PureTech Health will receive up to \$36 million, including upfront payments, research support, and early preclinical milestones. PureTech will be eligible for development milestone payments of over \$1 billion and additional sales milestones and royalties.

Notable: Another approach to the oral delivery of biologicals, in this case Roche's antisense oligonucleotides. The Calix Exosomes are extracellular cell-derived nanovesicles intended to deliver contents to the intestine where they can be absorbed. The milk-derived exosomes have evolved to permit oral transport of complex biological molecules, as well as small molecule drugs that are intrinsically not orally bioavailable.



Product: AXO-Lenti-PD

Indication: Parkinson's Disease

Product Stage: Preclinical

Licensors/Licensee: Oxford BioMedica/Axovant Sciences

Deal Value/Upfront: \$842 million/\$30 million

Deal Summary: Oxford BioMedica receives \$30 million upfront and is eligible to receive \$812 million upon the achievement of development, regulatory and sales milestones, plus 7% to 10% tiered royalties. Axovant will fund all clinical development and scale-up costs and receives full commercialization rights.

Notable: Significantly extended therapeutic activity. Referred to as second-generation gene therapy AXO-Lenti-PD is intended to deliver three genes that encode dopamine synthesis enzymes for a period of years.



Product: TOBI Podhaler and TOBI Solution

Indication: Cystic Fibrosis

Product Stage: Marketed

Licensors/Licensee: Novartis/Mylan

Deal Value (Total): \$463 million

Deal Summary: A simple transaction in which Mylan acquires the two assets worldwide in exchange for a staggered payment of about \$460 million.

Notable: The circle of life in the pharmaceutical business. First approved more than 20 years ago as an inhalation solution, and refreshed six years ago with the Podhaler formulation, the TOBI franchise is intended to provide support for Mylan's respiratory franchise.



Product: Inhaled formulation of treprostinil ("TreT")

Indication: Pulmonary Arterial Hypertension

Product Stage: Phase 1

Licensors/Licensee: MannKind/United Therapeutics

Deal Value/Upfront: \$45 million/\$95 million

Deal Summary: MannKind will manufacture clinical supplies and initial commercial supplies. United Therapeutics is responsible for global development, regulatory and commercial activities with respect to TreT. MannKind will receive an upfront payment of \$45 million, potential milestone payments of up to \$50 million, and low double-digit royalties.

Notable: MannKind, with their high-performance Technosphere technology has seemingly found a therapeutic target, and partner, capable of exploiting the commercial potential of the technology. It's also notable that Al Mann was an inventor of the MiniMed technology used with United Therapeutics first approved treprostinil product – Remodulin.



Product: Tau Program

Indication: Alzheimer's Disease

Product Stage: Preclinical

Licensors/Licensee: Voyager Therapeutics/AbbVie

Deal Value/Upfront: >\$1 billion/\$69 million

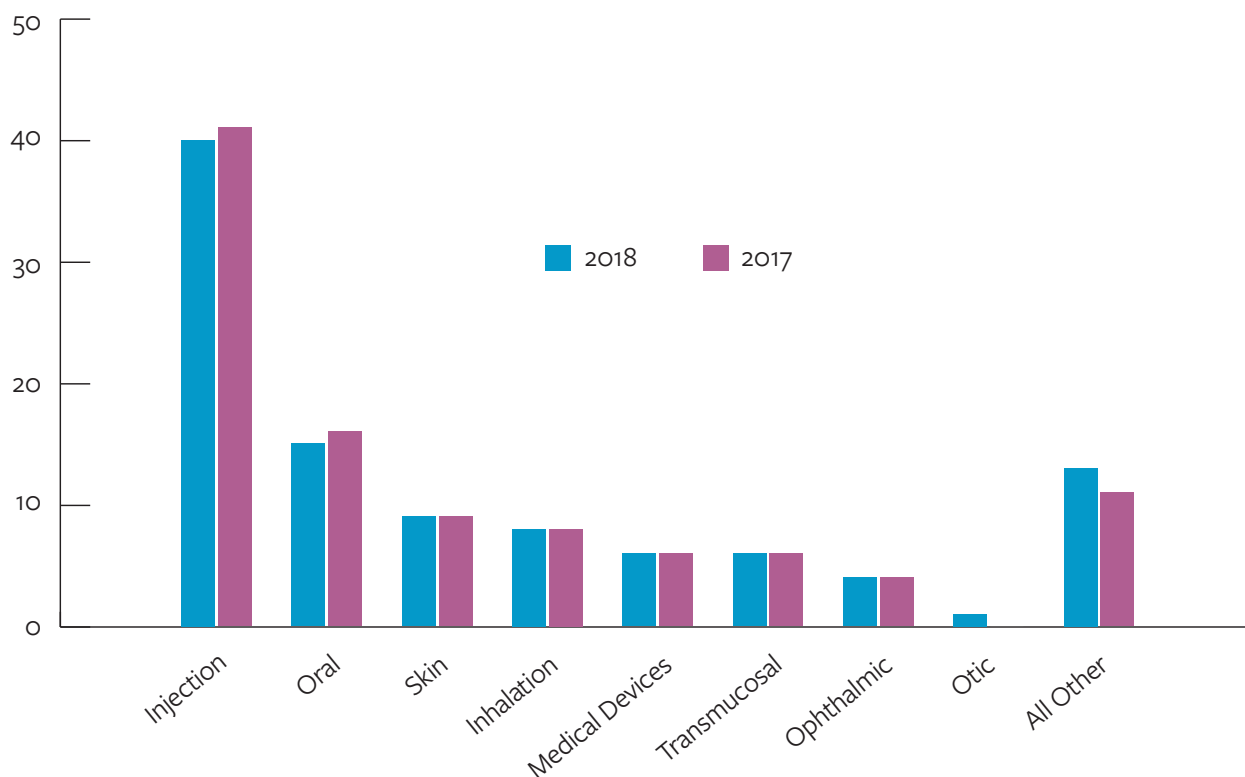
Deal Summary: Voyager will perform preclinical development of vectorized antibodies directed against tau and be responsible for costs up through Phase 1 studies. AbbVie has an option to lead further clinical development and commercialization. Voyager will receive an upfront payment of \$69 million and up to \$155 million in potential payments through Phase 1 and receive up to \$895 million in development and regulatory milestones, plus tiered royalties.

Notable: More barriers being crossed? This product deal sees the Voyager AAV9 variant technology that incorporates a modified gene fragment encoding for a small loop on the surface of the capsid of the virus being used to cross the blood-brain barrier and transduce the adult mouse brain following intravenous injection.



The Focus of Drug Delivery & Formulation Technologies Changed Little in 2018

Chart 1. Share of Active Drug Delivery and Formulation Technologies by Category



Source: PharmaCircle Drug Delivery Technology Analyzer Module

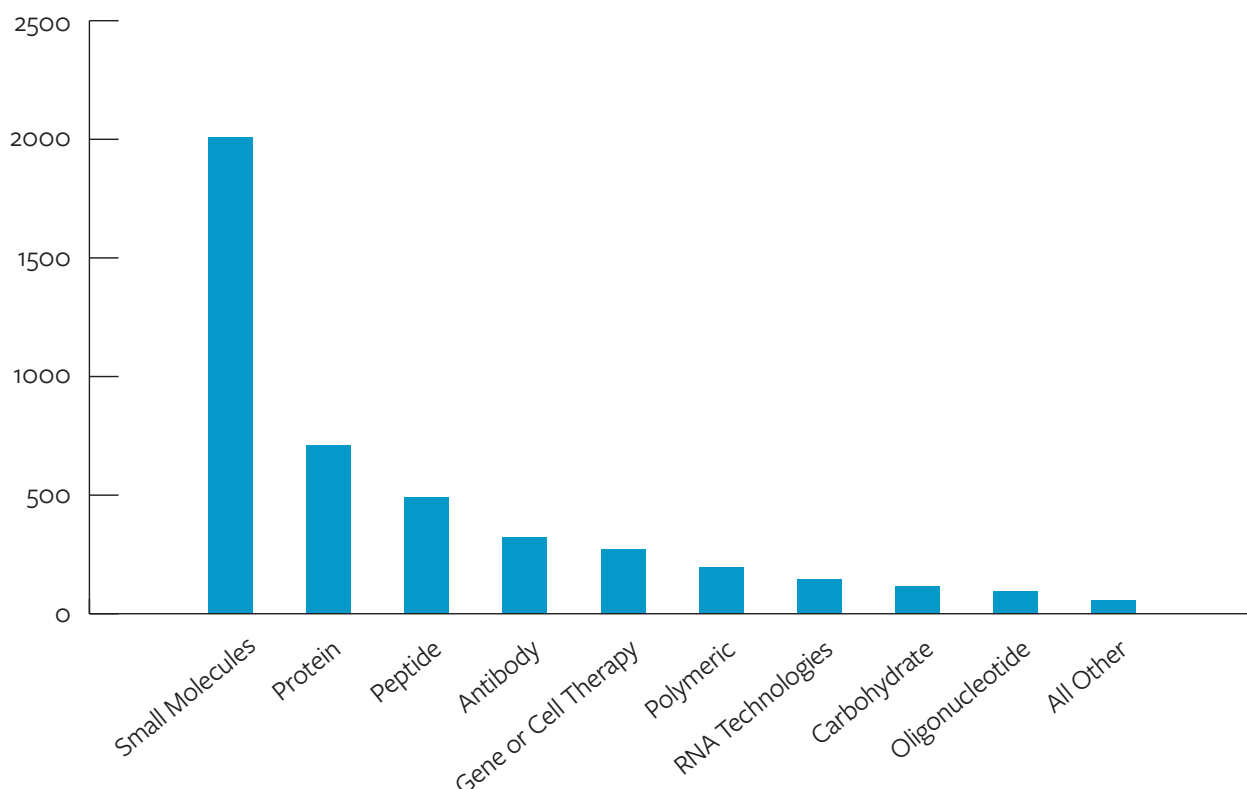
Chart Notes:

1. Only Active Drug Delivery and Formulation are included.
2. Technologies are summed by PharmaCircle Drug Delivery Categories. Technologies may be included in more than one Drug Delivery Category as appropriate.
3. Medical Devices refers to devices used for the delivery of pharmaceuticals, not standalone devices such as pacemakers.
4. All Other includes Compliance, Stabilization, Veterinary, 3D Printing and Implant technologies.
5. Data sourced March 2019 and March 2018

- There are 5,302 identified Active Drug Delivery Technologies (2019-03) versus 4,800 a year earlier.
- Of the 5,302 Active technologies, 2,177 are not associated with an identifiable pipeline product.
- Injection (40%) continues to be the most important area of technology development followed by Oral (15%) and Skin (9%).
- There were an additional 1,674 technologies identified by PharmaCircle as no longer being active.

Non Small Molecule Technologies Account for the Majority of Applications

Chart 2. Active Technology Applications by Molecule Type



Source: PharmaCircle Drug Delivery Technology Analyzer Module

Chart Notes:

1. Active drug delivery and formulation technologies only.
2. Technologies are summed by PharmaCircle Drug Delivery Categories. Technologies can be applicable to more than one Molecule Type.
3. RNA Technologies include siRNA, mRNA, miRNA.
4. All Other includes Virus, Stem Cell Microbiome and Tissue.
5. Data sourced March 2019.

- Of the identifiable molecule applications, 2007 technologies were applicable to Small Molecules.
- As a group there were 2,409 active technologies applicable to non-small molecule actives.
- Antibodies showed one of the largest year over year increase, percentage wise, in active technologies.
- Active RNA technologies, up 25%, also showed a strong year over year increase.

Notable Drug Delivery and Formulation Technologies of 2018

Technology: Triozan

Nanomedicine
Delivery Platform

Application(s): Oncology,
CNS, Antibiotic Resistance

Most Advanced Stage: Preclinical

Technology Category(s): NP polymer, Tight
Junction Modifiers, Oral Peptide/Protein/
Macromolecule, Brain Targeting, Nasal Formulations

Company: Ovensa Inc.

Notable Pipeline: TRIOZAN/PTX Oral
(Preclinical, Oncology)

Technology Summary: A chitosan based nanocarrier that can reach the brain via oral dosing with large molecules/biologics. TRIOZAN can cross various membranes opening the possibility for other routes of delivery (nasal, inhalation, ophthalmic, buccal etc.). Triozan formulated therapeutics can also be stored intracellularly for example in tumors, and act as a reservoir for long term release.

Notable: Old becomes new again with this new twist on chitosan-based carriers to improve delivery to various cell and tissue types. A recent agreement with Takeda, March 2019, is focused on delivering antibodies to the brain.



Technology: G-Technology

Application(s): Brain
Diseases, Retinal Diseases

Most Advanced Stage: Phase 2

Company: 2-BBB Medicines

Notable Products: 2B3-101 (Phase 2, Brain Cancers),
2B3-201 (Phase 1, Multiple Sclerosis)

Technology Summary: A PEGylated liposomal technology with glutathione as a targeting ligand at the ends of the PEG molecules to mediate safe targeting and sustained delivery of systemically administered across the blood-brain and blood-retinal barriers. Liposomal delivery increases the metabolic stability while PEGylation increases the plasma half-life of the active which is loaded into the center of the liposome.

Notable: Technologies such as G-Technology are increasingly demonstrating the ability to effectively and efficiently deliver actives across the blood-brain and blood-retinal barriers to treat challenging brain conditions. A partnership with Mireca Medicines has a preclinical candidate in development for retinal disease.



Technology: OraFuse

Application(s): Multiple

Most Advanced Stage: Phase 2

Company: SynAgile

Notable Products: DopaFuse Oral Paste
(Phase 2, Parkinson's Disease)

Technology Summary: A proprietary miniature, disposable, intraoral delivery system carried on a small tooth-attached retainer that continuously infuses medication into the mouth. The device can incorporate a variety of stop/start mechanisms.

Notable: A technology that can provide an infusion type constant delivery through the oral route but unlike the current buccal systems that attach to the inner cheek and which have had relatively limited market acceptance.



Technology:

Print Ocular Implant

Application(s): Ophthalmic Diseases

Most Advanced Stage: Phase 2

Company: Aerie Pharmaceuticals

Notable Products: AR-1105 Implant
(Macular Edema, Phase 2)

Technology Summary: A precision nanomoulding technology platform for ocular sustained release drug delivery that uses imprint lithography techniques and DSM polyesterimide polymers to produce monodisperse (uniform) nano (or micro) particles. These polymers are liquid at room temperature and are UV-cured to form clear "PTFE-like" elastic solids.

Notable: Aerie's implants are remarkably versatile as they can be administered to the posterior (intracameral, intravitreal) and anterior (subconjunctival) segment of the eye to deliver most actives.

