2019 Global Drug Delivery & Formulation REPORT

Part Three of a Four-Part Series

Part 1: A Review of 2019 Product Approvals

Part 2: Notable Drug Delivery and Formulation Product Approvals of 2019

Part 3: Notable Drug Delivery and Formulation Transactions and Technologies of 2019

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Introduction

It was not so long ago when the drug delivery business model was "simple." Big Pharma discovered the drug, and drug delivery companies provided the means to optimize its performance. Big Pharma took the risks of clinical development and commercialization, and reaped the rewards while drug delivery companies contented themselves with license fees, milestones, royalties, and hopes of landing additional partners for the same platform. The script has been flipped with the genomic revolution. For diseases with a well-understood genetic cause, discovering the "drug," increasingly some sort of nucleic acid derivative, is becoming increasingly obvious. The real challenge is delivering these generally fragile therapeutics both safely and in sufficient amounts to very specific locations in very specific cells. No longer is drug delivery and formulation an improvement, it is a necessity.

Following a generation of technology commoditization, Big Pharma is once again looking for technologies to deliver these new therapeutics. Their preferred business model in dealing with "delivery" companies remains the same; license fees, milestones, and single-digit royalties, but these "delivery" companies, eschewing the label of Drug Delivery, are increasingly looking for a bigger piece of the action. With the success of smaller companies developing and commercializing new-generation therapeutics, Big Pharma has been forced to sweeten the deal.

This doesn't mean there aren't technology opportunities for small molecule therapeutics, but the opportunities and rewards have shrunk as technologies lose exclusivity and Big Pharma brings the necessary expertise in-house. The business for low-margin technologies has shifted to Service Companies that are content with lower license-related fees in exchange for manufacturing and packaging margins.

This year, nine technologies were identified as "notable" by the Technology Team: Alnylam's ESC-GalNAc-Conjugate Delivery, Emisphere's Eligen Technology, RegenexBio's NAV Vectors, PharmaCyte's Cell-in-a-Box, DBV's ViaSkin, Ensai's ImplaVax, Beta Bionics' iLet Bionic Pancreas, Lyndra's GR Oral Delivery, and Mati's Punctal Drug Delivery. Of these, four are presented in more detail later in this review.

On the deal front, perhaps Dicerna's deal with Novo Nordisk and Codiak Biosciences' agreement with Jazz Pharmaceuticals, which are discussed further, best represent the new reality. Honorable mention goes out to Halozyme who inked another attractive Enhanze licensing deal with Argenx after stepping back from developing their own proprietary pipeline. Sometimes you need to play to your strengths.

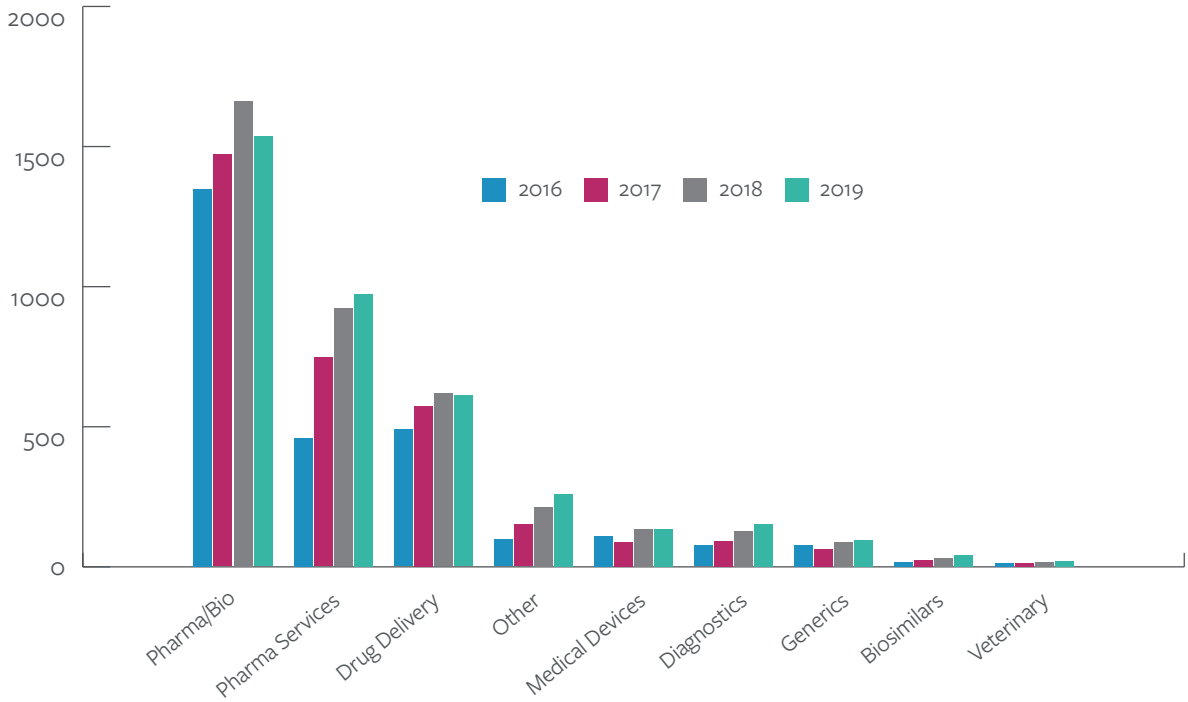
Notable Drug Delivery and Formulation Related Technology Transactions of 2019

Technology: engEx Platform
Indication(s): Cancer
Delivery Route: Injection
Licensor: Codiak Biosciences
Licensee: Jazz Pharmaceuticals
Deal Value/Upfront: Potentially >$1 billion/$56 million
Royalty: Mid-Single to High-Teens
Deal Summary: A strategic collaboration agreement focused on the research, development, and commercialization of exosome therapeutics to treat cancer. Codiak granted Jazz an exclusive, worldwide, royalty-bearing license for therapeutic candidates directed at five targets to be developed using Codiak's engEx platform. The targets include well-validated oncogenes implicated in hematological malignancies and solid tumors, but have proven to be largely undruggable. Codiak is responsible for the execution of preclinical and early clinical development of therapeutic candidates through Phase 1/2 proof-of-concept studies, Jazz thereafter. Codiak has an option to participate in co-commercialization and cost/profit-sharing in the US and Canada for up to two products. Codiak will receive an upfront payment of $56 million, up to $20 million in preclinical development milestone payments, and milestone payments totaling up to $200 million per target, plus tiered royalties.
Notable: This is not unlike "classical" drug delivery technology deals in which the licensor provides its proprietary delivery technology for application to the licensee's specified actives. The difference here is that Codiak seems responsible for the therapeutic active as well. The engEx technology can incorporate a range of therapeutic drug classes (including small molecules, proteins, peptides, cytokines, and nucleic acids) onto the surface or in the lumen of its therapeutic exosomes. The exsomes can also be engineered to optimize potency and tropism for directed delivery to desired cell types.

Technology: GalXC RNAi Platform
Indication(s): NASH, Type 2 Diabetes, Rare Diseases
Delivery Route: Injection
Licensor: Dicerna Pharmaceuticals
Licensee: Novo Nordisk
Deal Value/Upfront: Potentially >$1 billion/$225 million (including equity)
Royalty: Mid-Single to High-Teens
Deal Summary: The agreement is for the discovery and development of novel therapies for the treatment of liver-related cardio-metabolic diseases using the GalXC RNAi platform technology. Dicerna will conduct and fund discovery and preclinical development to clinical candidate selection for each liver cell target, and Novo Nordisk will be responsible thereafter. Dicerna receives an upfront payment of $175 million, a $50 million equity investment, $25 million annually during each of the first 3 years of the collaboration, and up to $357 million per target in milestone payments, plus tiered royalties on sales ranging from the mid-single-digits to mid-teens.
Notable: This is the second agreement signed by Dicerna with heavyweight Big Pharma companies within a month. The earlier agreement with Roche was for similar terms and targeted to Chronic Hepatitis B. The challenge addressed by Dicerna's GalXC RNAi platform is the efficient delivery of siRNA and oligonucleotide therapeutics to the targeted RNAi machinery. With the GalXC RNAi platform the challenge is handled by means of GALNAc sugars attached to the extended region of a proprietary Dicer substrate short-interfering RNA (DsiRNA-EX) molecule.

Transactions in the Pharma Sector Largely Flattened Out in 2019

Chart 1. Pharma-Related Transactions by Category (2016-2019)



Source: PharmaCircle Strategic Deals Module

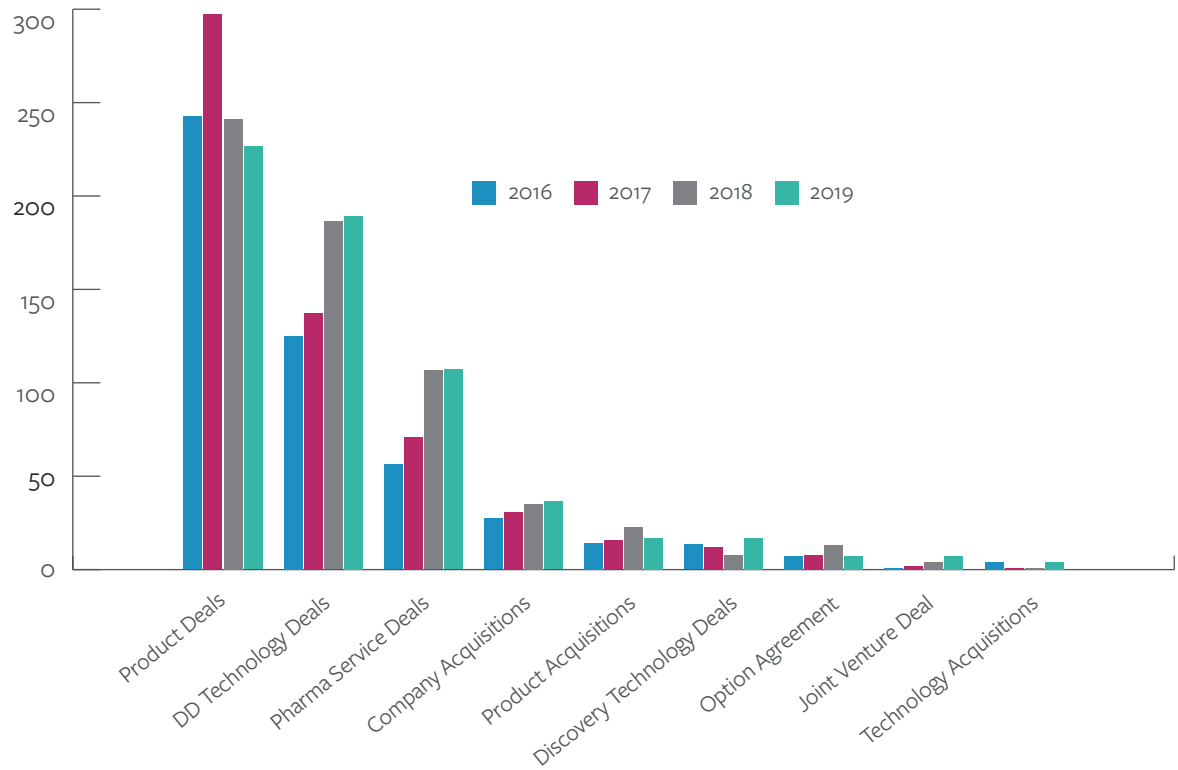
Table notes: Transaction assignments are made by PharmaCircle analysts. The transaction numbers do not include amendment or termination agreements that generally account for 10%-15% of all transactions.

This chart summarizes announced transactions, excluding termination and amendment agreements, for the past 4 years. Transactions in general showed a sharp uptick in 2017 (+20%) and 2018 (+18%) that flattened out in 2019 (0%).

- Pharma/Bio transaction totaled 1,533 in 2019 versus 1,660 in 2018.
- Pharma Services transactions continued to climb in 2019 with a total of 974 announced deals. This reinforces the sense that companies are doing more and more outsourcing, especially for access to more specialized services like vector production. The service companies are doing their part to accommodate the needs with announced expansions of facilities and the acquisition of smaller, more specialized, technology-focused companies.
- Drug Delivery transactions, 610 in 2019, have largely remained constant after a jump of 17% in 2017.
- Medical Device transactions, only those related to patient managed pharmaceutical administration, have remained relatively flat over the past few years.

Drug Delivery Technology Transactions Remained Robust in 2019

Chart 2. Drug Delivery Transactions by Transaction Type (2016-2019)



Source: PharmaCircle Strategic Deals Module

Table notes: Transaction assignments are made by PharmaCircle analysts. The numbers do not include amendment or termination agreements that generally account for 10%-15% of all transactions.

Drug Delivery-related transactions totaled 610 in 2019, little changed from 2018 (-1%), largely paralleling the overall Pharma trend. This was a change from the solid increases experienced in both 2017 (+17%) and 2018 (+8%).

- Product Deals fell in 2019 (226) falling well short of the 297 in 2017. There has been less interest on the part of drug delivery companies to take the expense and risk of developing products to advanced stages in hopes of licensing them out. Recent experience has not been kind to drug delivery companies that ventured out into product development with limited commercial success or outright portfolio failures (Nektar and Halozyme).
- The solid figures for Drug Delivery Technology Deals seen in 2019 were in large part accounted for by biologicals with an increase in gene and cell therapy-related technologies.
- The Pharma Services transactions were not necessarily associated with traditional drug delivery companies, but rather service companies that have acquired or developed their own suite of technologies and capabilities.
- Technology Acquisitions accounted for effectively nothing in 2019 (four transactions) as product development companies preferred to acquire technologies as part of a larger company acquisition or by contracting with Service Companies.

Notable Drug Delivery & Formulation Technologies of 2019

Technology: Alnylam ESC-GalNAc-Conjugate Delivery
Most Advanced Stage: Marketed (US, Europe)
Technology Category(s): Conjugates, Carbohydrate, Receptor/Carrier, Liver Targeting, Brain Targeting
Company: Alnylam Pharmaceuticals
Notable Pipeline: Lumasiran (Alnylam) Registration

Technology Summary: The technology uses novel carbohydrate conjugates and RNAi agents to target the parenchymal cells of the liver. RNAi is conjugated to an asialoglycoprotein receptor (ASGPR) ligand derived from N-acetylgalactosamine (GalNAc) via a cleavable linker. The Enhanced Stabilization Chemistry (ESC)-GalNAc-conjugate delivery platform enables subcutaneous dosing of RNAi therapeutics with increased potency and durability, and a wide therapeutic index. Once-monthly and less-frequent SC dose regimens might be possible. The technology is based on the discovery that conjugation of a carbohydrate moiety to an RNAi agent can optimize one or more properties of this agent. For example, the ribose sugar of one or more ribonucleotide subunits of an RNAi agent can be replaced with another moiety, ie, a non-carbohydrate (preferably cyclic) carrier to which a carbohydrate ligand is attached. The carbohydrate ligand is selected specifically as GalNAc for liver targeting.

Notable: This technology is the first and only one among GalNAc-RNAi conjugate technologies to have received regulatory approval, November 2019 in the US and March 2020 in Europe, (GIVLAARI for the treatment of acute hepatic porphyria). The technology has been tested for other delivery routes including oral and ocular with promising results reported for CNS delivery.

Technology: iLet Bionic Pancreas by Beta Bionics
Most Advanced Stage: Phase 2
Technology Category(s): Insulin Pumps, Combination/Incompatible, Drug Delivery Compliance
Company: Beta Bionics
Notable Pipeline: iLet Bionic Pancreas, Insulin Only (Novo Nordisk) Phase 2, Dasiglucagon Dual-Hormone Pump Therapy (Zealand Pharma) Phase 2

Technology Summary: The iLet is a pocket-size, wearable medical device that autonomously controls blood sugar in people with diabetes and other conditions. The iLet is a bihormonal system leveraging machine learning and artificial intelligence to deliver insulin and glucagon analogs for the autonomous treatment of Type 1 Diabetes. In addition to dosing insulin, the iLet doses dasiglucagon, a glucagon analog with a unique stability profile in a ready-to-use aqueous solution.

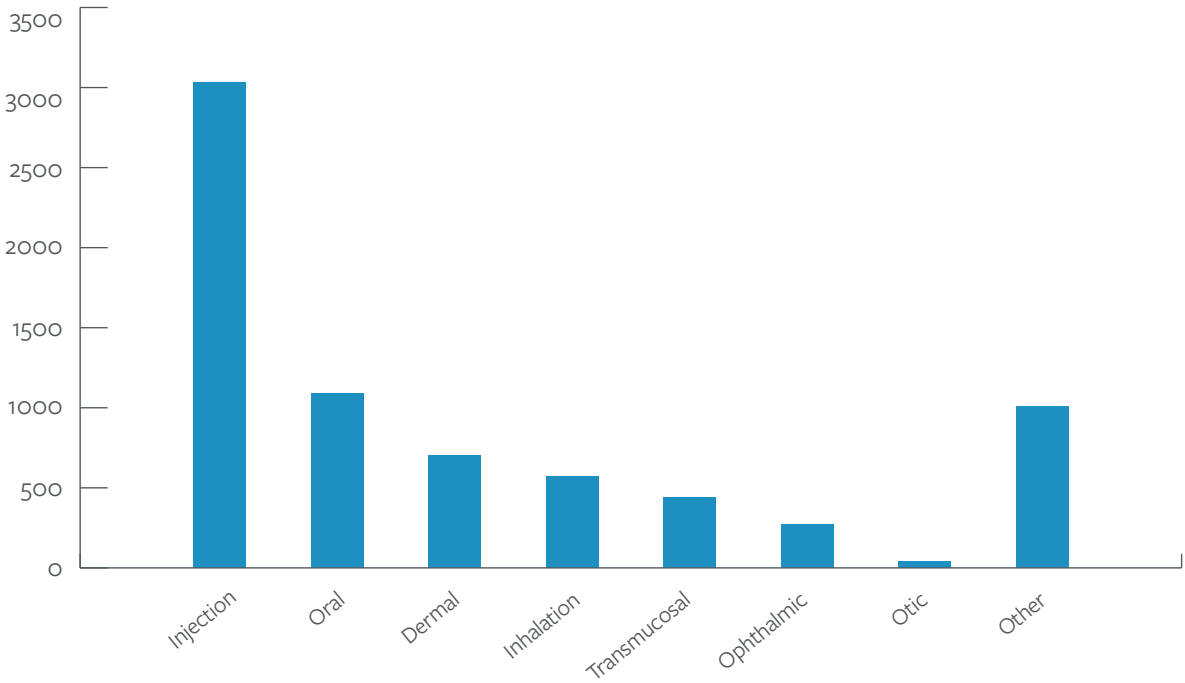
Notable: In 2019, unprecedented glycemic control was demonstrated in a first Phase 2 home-use clinical trial testing the iLet Bionic Pancreas with dasiglucagon for autonomous management of T1D. There was no device training period and no physician intervention to optimize therapy. In December 2019, Beta Bionics received Breakthrough Device designation from the FDA for the iLet Bionic Pancreas System in all configurations (insulin-only, glucagon-only, and bihormonal).

Technology: Lyndra GR, Oral Ultra Long-Acting Drug Delivery
Most Advanced Stage: Phase 1
Technology Category(s): Gastro Retentive, 3D Printing
Company: Lyndra Therapeutics
Notable Pipeline: Lyndra Ivermectin (Malaria) Phase 1, LYN-057 (Alzheimer's) Phase 1
Technology Summary: A polymeric, multi-arm device that unfolds and expands to assume a star shaped geometry when delivered to the stomach in a capsule. Upon entering the stomach, the multi-arm configuration extends, preventing further passage through the GI tract, allowing gastric residence for 7 days, potentially longer. The Lyndra GR technology enables ultra-long-acting oral therapeutic delivery, delivering small molecule therapies weekly and potentially monthly. The novel internal microarchitectures are achieved with 3-D printing technology. The arm linkages break/dissolve based on hydration pH to deliver compound in the stomach. The active is released from the system through controlled polymer matrix release technology. Following breakdown, the device residue is safely passed through the gastrointestinal system.
Notable: The technology is the result of work in the Langer lab at MIT with early and ongoing funding from the Gates Foundation. Despite the many oral sustained-release products available, there remains a significant need for therapeutics and the underlying technologies that can further simplify oral dosing particularly for compliance challenged indications. The technology may also be applicable to other delivery routes including urethral, rectal, intrauterine and vaginal.

Technology: ImplaVax
Most Advanced Stage: Phase 1
Technology Category(s): Needle-Free Injectors, Reusable, Solid Dose Injectors, Biodegradable Non-PLGA Microcaps/Implants
Company: Enesi Pharma
Notable Pipeline: Shigella Vaccine (Walter Reed Army institute) Phase 1, Mumps Rubella Vaccine (Gates Foundation) Preclinical
Technology Summary: Enesi Solid Dose Injector (SDI) is a novel spring- powered needle-free injector allowing the injection of solid formulations. For vaccine delivery applications, this device/formulation combination platform is called ImplaVax. The SDI utilizes a disposable, dissolvable tip/drug cassette combination that can create a channel in the skin prior to the delivery of the drug. Features include automatic actuation and resetting mechanisms.
Notable: ImplaVax-enabled solid dose vaccines have the potential to eliminate the need for reconstitution as well as needlestick and cross-contamination hazards. Improved thermal stability would also be a major added benefit in countries where cold-chain issues and access to target populations for vaccinations can be challenging. The company has received grant funding from the Bill & Melinda Gates Foundation to support a new project to evaluate ImplaVax technology platform for enabling the development and delivery of solid dose vaccines for Measles and Rubella. In February 2020, ImplaVax was nominated in the Best New Vaccine Technology/Platform category, at the 13th Annual Vaccine Industry Excellence (ViE) Awards.

Injection Continues to be the Focus of Technology Development

Chart 3. Active Technologies by Drug Delivery Category



Source: PharmaCircle Drug Delivery Technology Analyzer Module mid-March 2020.

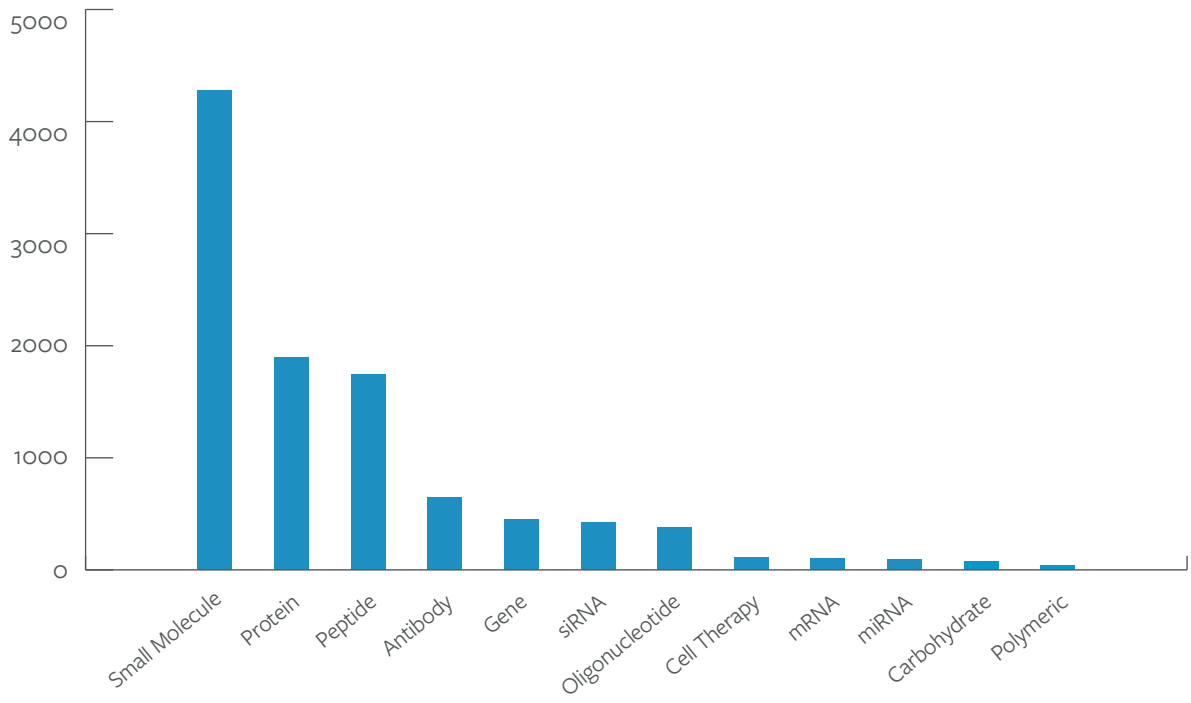
Table notes: Technology assignments are made by PharmaCircle analysts. Only technologies identified as currently active are included. Technologies can be applicable to more than one Route. Other includes a variety of technologies, such as compliance, stabilization, and production processes.

Injection technologies unsurprisingly continue to represent the largest number of active technologies perhaps because of fewer physical limitations, such as molecule size, bioavailability, stability, that represent significant challenges for other delivery routes.

- PharmaCircle has identified 5,650 discrete active drug delivery and formulation technologies. There are an additional 1,827 technologies that are considered to be inactive.
- Some 3,030 technologies are applicable to delivery by Injection. About 1,650 of these technologies are being used in products that are identified as approved or in active development at a research, preclinical, or clinical stage.
- There are 1,090 technologies applicable to Oral delivery of which 630 are associated with one or more products that are approved or in development.
- The number of active technologies applicable to Transmucosal (442) is somewhat surprising given the relatively small number of products and opportunities.
- Other refers to a variety of technologies that are not directly assignable to a delivery route and span a range of applications from compliance to super critical fluids to low dose formulations

Small Molecules Unsurprisingly Are Associated With the Most Active Technologies

Chart 4. Active Technologies by Molecule Type



Source: PharmaCircle Drug Delivery Technology Analyzer Module mid-March 2020.

Table notes: Technology assignments are made by PharmaCircle analysts. Only technologies identified as currently active are included. Technologies can be applicable to more than one Molecule Type.

Somewhat more surprising is the number of active drug delivery and formulation technologies that are identified as being applicable to peptides considering the relatively few peptide based products approved and in development.

- There are 4,282 active technologies identified as being applicable to small molecule pharmaceuticals. Almost exactly half, 2,138, are identified as being associated with one or more approved products or products in active development.
- 1,879 protein and 1,740 peptide applicable technologies have been identified. They are associated with 734 and 492 products respectively that are approved or in active development.
- There is a considerable drop-off in the number of active technologies applicable to antibody (651), gene (447), siRNA (425), oligonucleotide (383) and cell therapy (114) therapeutics.

Becton, Dickinson Leads all Companies with 69 Active Technologies

Table 1. Top Three Technology Companies by Route

Route (Number of Technologies)	Company	Active Technologies by Route	All Active Technologies
Inhalation (573)	Philips Respironics	29	35
	Vectura	20	30
	Pari	18	18
Injection (3,034)	Becton, Dickinson	63	69
	SHL	34	34
	Ypsomed	31	31
Ophthalmic (273)	EyePoint	10	13
	Alcon	10	10
	Allergan	9	11
Oral (1,091)	Teva	25	50
	Capsugel	19	22
	Catalent	16	24
Otic (56)	Aero Pump	3	7
	Mystic	3	8
	Silgan	3	7
	Ursatec	3	7
Dermal (702)	LTS Lohmann	13	16
	Foamix	10	11
	Corium	7	9
	Inovio	7	17
	Nemaura	7	8
	DJO Global	7	7
Transmucosal (442)	Aptar	16	27
	Silgan	6	7
	Nemera	5	14
	Teva	5	50
	Aero Pump	5	7
	Ursatec	5	7
	Mystic	5	8
All Technologies	Becton, Dickinson		69
	Teva		50
	Philips Respironics		35

The drug delivery and formulation space is characterized by multiple companies competing in each delivery route, with most specializing in one or at most two areas.

- Two companies that work at the interface of devices and pharmaceutical delivery, Becton, Dickinson (Injection) and Phillips Respironics (Inhalation), are the number one and three companies in terms of identified active technologies.
- Perhaps surprisingly, Teva sits in the number two position with multiple technologies in a variety of areas, including Oral, Inhalation, Injection, and Transmucosal.
- Service Companies like Aptar (27) and Catalent (24) are associated with leading positions in terms of drug delivery and formulation technologies.