2020 Global Drug Delivery & Formulation

REPORT

Part Three of a Four-Part Series

Part 1: A Review of 2020 Product Approvals

Part 2: Notable Drug Delivery and Formulation Product Approvals of 2020

Part 3: Notable Drug Delivery & Formulation Transactions and Technologies of 2020

Part 4: The Drug Delivery and Formulation Pipeline

By: Kurt Sedo, Vice President Operations, and Esay Okutgen, Ph.D., Director Drug Delivery, PharmaCircle LLC

Introduction

There are only a limited number of plots or scales when it comes to movies and music. That is of course until something new is discovered and everyone quickly follows. It is much the same with drug delivery and formulation. Everyone was all in on oral sustained-release delivery and transdermals until the opportunities dried up. This was followed by injectables, notably longer-acting injectables. More recently, the drug delivery and formulation technologies that have captured the interest of pharmaceutical companies revolve around the use of injectables in the outpatient market. These technology shifts have largely arisen in response to the changing product opportunities presented with new molecular motifs and commercial realities. Transdermal and oral sustained release provided clinical and business opportunities for the large inventory of small molecule actives that could benefit from dose modification. Long-acting injectable technologies were a response to the emerging macromolecule and biologics sector. The development of more convenient injection technologies for outpatient use was less a response to a therapeutic challenge than a commercial opportunity. Office or hospital cased injections were not only more costly, but also inconvenient to providers and patients.

It seems that the latest evolution in pharmaceutical products is on par with the transition from small molecule oral therapeutics to macromolecules, proteins, and antibodies. The recognition that RNA represents a significant therapeutic motif has required the development of technologies that can effectively deliver these molecules to very particular cellular targets. At the same time, there is a growing confidence that gene and cell therapies can provide similar benefits with longer horizons. These new products also require effective and efficient drug delivery and formulation technologies to ensure efficacy, safety, and stability.

In terms of transactions, while the numbers jumped in 2020, the deals largely used the same commercial templates as in previous decades. An exception might be the increasing number of deals announced that involve companies selling future milestone and royalty revenues in exchange for upfront cash. Drug delivery and formulation technologies in 2020 were a mix of the old and new, and their importance was reinforced. As we saw in 2020, even something as seemingly trivial as relaxing storage and transportation temperatures or larger vial sizes can make a big difference in terms of impacting a global pandemic.

2010s Technologies of the Decade - Subcutaneous Injectables

If the 1980s through 1990s were the decades of transdermal and extended- release oral technologies, and the 1990s through 2000s were the decades of PEGylation and injectable depot technologies, we can with some confidence declare the 2010s the decade of subcutaneous injectable technologies.

With the development and approval of a wide range of biologics possessing intrinsic long-acting properties, the therapeutic and commercial opportunity that quickly became apparent was making these therapeutics more convenient for patients and the healthcare system. Biologics can generally be readily administered without much complexity using an intravenous route of delivery. Too often, this requires in-patient administration that can demand hours-long infusions with complex dose ramping. Moving these often chronically administered biologics to out-patient use requires rerigging the products, preferably with limited formulation adjustments to simplify regulatory requirements and to reduce any chance of a clinical surprise.

The solution began to appear in the 2000s with the development of subcutaneous injection devices that not only simplified out-patient dosing with single-dose injectors, but also removed the intimidation of a typical needle. The opportunity that largely pushed this development was the increasing use of insulin for the treatment of Type 2 diabetes. While patients with Type 1 diabetes had long resigned themselves to drawing up a dose and injecting subcutaneously for the rest of their lives, Type 2 patients were intimidated by the process of doing dose calculations and going through the injection process.

These single and multidose injectors were soon adopted for low-volume biologicals that required injection as often as daily or as infrequently as monthly. These injectors not only met a pressing therapeutic need, but also accelerated the adoption of these biological products in the out-patient setting. Products like AbbVie's Humira and Amgen's Enbrel have managed to achieve multibillion dollar annual sales even though they require patient self-injection.

Despite the acceptance of these devices, there remained a significant therapeutic gap and commercial opportunity. These pen devices were generally limited to the injection of relatively small volumes, on the order of 1 ml or less. This limited the opportunities for products that required larger volumes for a variety of reasons, including stability and viscosity. The prospect of multiple individual doses was not an appealing option.

The solution to this challenge was provided by Halozyme and their Enhanze technology, a drug delivery system that uses high-dose recombinant human hyaluronidase PH20 enzyme (rHuPH20) co-administered subcutaneously along with the therapeutic, either sequentially or with co-formulation. The enzyme degrades hyaluronan [sodium hyaluronate or hyaluronic acid (HA)], a polysaccharide found within the extracellular matrix. Degradation of hyaluronan at the local injection area allows dispersion and absorption of the therapeutic agent more easily and rapidly and is restored via normal processes within 24-48 hours. The Enhanze technology permits large- volume administration, 2-20-ml subcutaneous injections, and up to 600-ml subcutaneous infusion.

Notable approved products utilizing Enhanze include:

- Genentech (Roche) - Herceptin SC/Herceptin Hylecta
- Biogen / Roche - Rituxan Hycela/MAbThera
- Baxalta (Takeda Pharmaceutical) - HyQvia
- Genentech (Roche) - Phesgo FDC
- Janssen / Genmab - Darzalex FASPRO

Surprisingly, for the better part of a decade, Halozyme has been the sole provider of high-volume subcutaneous formulation technology. Year after year, Halozyme has been signing deals with new and existing partners to extend the use of the Enhanze technology, but there may be some competition in the wings with Arecor's Arestat technology.

If the 1980s and 1990s were defined by transdermal and long-acting oral technologies, the 1990s and 2000s by PEGylation and long-acting injectable depot technologies, and the past decade by subcutaneous injection devices and technologies, what comes next? The early favorites are gene and cell technologies along with RNA delivery technologies.

Notable Drug Delivery and Formulation Technologies of 2020

Technology: NAV Technology Platform
Most Advanced Stage: Marketed
Technology Category(s): Adeno-Associated Virus Vectors
Company: REGENXBIO
Notable Pipeline: Zolgensma (SMA, Marketed, Novartis), RGX-314 (Wet AMD, Phase 2)
Notable: A foundational technology for gene delivery.
Technology Summary: The NAV Technology Platform consists of over 100 novel adeno-associated virus (AAV) vectors, including AAV7, AAV8, AAV9, AAVhu68 (AAV9 variant), and AAVrh10 (NAV Vectors), applicable to the delivery of genetic materials to targeted cells. Inside the cell nucleus, the NAV capsids dissolve and release a gene that is transcribed into RNA and encoded into the desired protein. NAV Technology provides advantages beyond "traditional" AAV, including more efficient delivery, a quicker onset of gene expression, higher tissue selectivity, and high titer manufacturing.

Technology: Clearside SCS Microinjection Platform
Most Advanced Stage: Registration
Technology Category(s): Ocular Delivery Devices/Dispensers, Specialty Syringes, Poration, Microneedles, Low-Dose Formulations
Company: Clearside Biomedical
Notable Pipeline: Xipere (Macular Edema, Registration, Bausch), CLSAX (Wet AMD, Phase 1/2)
Notable: A new administration site for the treatment of ocular diseases.
Technology Summary: The technology uses a hollow microneedle to deliver drugs via controlled infusion directly to the suprachoroidal space (SCS, space between the sclera and choroid), which has only been accessible through surgical techniques. There is no limitation on the types of drugs that can be administered with the technology. Administration can be targeted to the posterior region to permit flow circumferentially toward the retinochoroidal tissue, macula, and optic nerve in the posterior segment of the eye. Particle size is critical as 20-nm particles readily spread in the SCS and within the sclera, while 1000-nm particles are retained primarily in the SCS.

Technology: TransCon - Transient Conjugation
Most Advanced Stage: Registration
Technology Category(s): Conjugates, PEG Polymer
Company: Ascendis Pharma
Notable Pipeline: TransCon hGH (Growth Disorder, Registration), TransCon PTH (Hypoparathyroidism, Phase 3)
Notable: A technology that may improve upon, and expand the applicability of, PEGylation.
Technology Summary: TransCon molecules have three components: an unmodified parent drug, an inert carrier, and a releasable linker. When linked, the carrier inactivates and shields the parent drug from clearance. After administration, the physiologic pH and temperature conditions initiate the release of the active, unmodified parent drug in a predictable release manner. Because the parent drug is released unmodified with no residual linker, it retains its native activity. The technology can use linear, branched, and multi-arm PEG (TransCon PEG). The TransCon technology can be applied broadly to proteins, peptides, and small molecules. The reversible linker chemistries are designed to provide predictable rates of autohydrolysis in vivo.

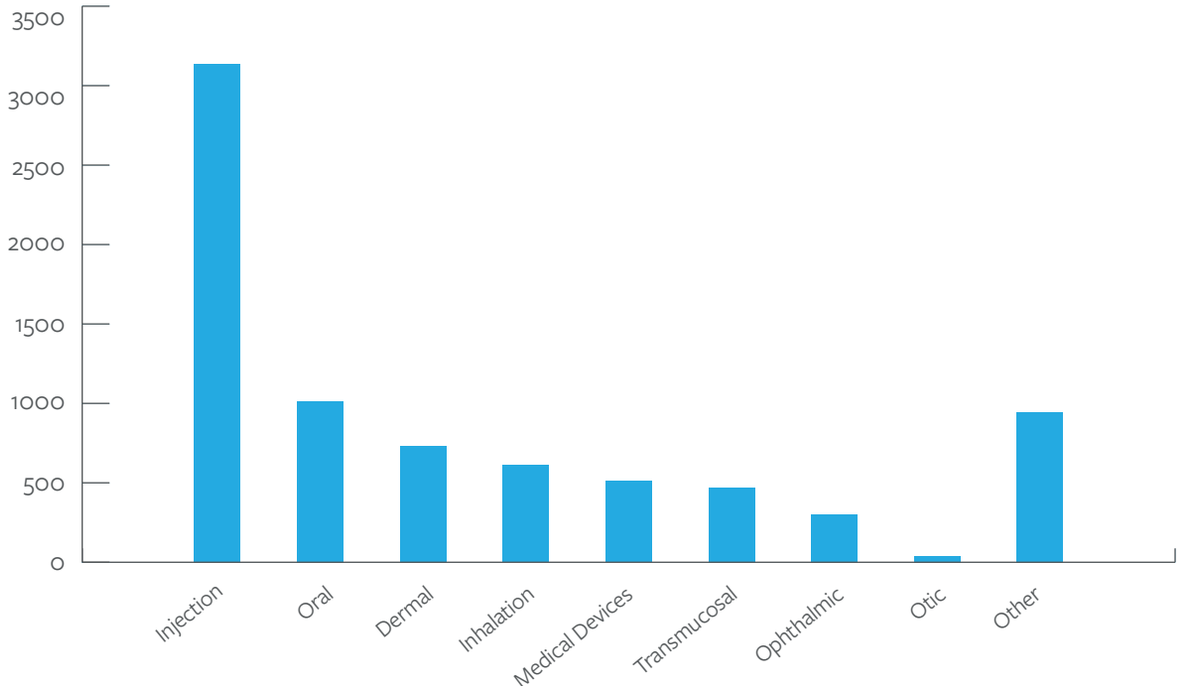
Technology: BEPO
Most Advanced Stage: Phase 3
Technology Category(s): Biodegradable Gel/Suspension
Company: MedinCell
Notable Pipeline: mdc-IRM (Schizophrenia, Phase 3, Teva), mdc-CWM (Pain Inflammation, Phase 2, Arthritis Innovation Corp.)
Notable: Perhaps the next-generation PLGA-based depot technology.
Technology Summary: A PLA/PEG/PLA based in-situ forming hydrogel depot system composed of a mono-dispersed network of hydrophilic chains (PEG) linked with hydrophobic micro-domains (PLA), which can entrap hydrophilic macromolecules. The hydrophobic micro-domains are able to solubilize and retain hydrophobic substances. Ten day to six-month release of small molecules and one-week release of peptides have been demonstrated.

Technology: Arestat
Most Advanced Stage: Phase 1
Technology Category(s): Stabilization Technologies, Concentrated Suspension/Viscous Solution, Rapid Acting Injectables
Company: Arecor
Notable Pipeline: AT247 (Diabetes, Phase 1), AT278 (Diabetes, Phase 1)
Notable: A potential alternative to Halozyme's Enhanze for larger volume subcutaneous injections.
Technology Summary: The Arecor technology provides the stabilization of proteins/biologics when stored under non-refrigerated conditions, even during storage at elevated temperatures and in higher concentrations for 12 months or longer. Arestat reduces the viscosity of biologic formulations, enabling higher concentration doses in easy-to-administer formats. It also enables liquid-stable versions of live-virus containing products that are used in vaccine and gene therapy products in liquid presentations at usual cold chain temperatures. The technology's lead products AT247 and AT278 provide an ultra-rapid onset of action of insulin while ensuring product stability.

Technology: MIMIX
Most Advanced Stage: Preclinical
Technology Category(s): Poration, Dissolvable Microneedle, Solid Dose Injectors, Biodegradable Non-PLGA Microcaps/Implants
Company: Vaxess Technologies
Notable Pipeline: Flu Vaccine (Preclinical), COVID-19 Vaccine (Preclinical)
Notable: A potentially improved delivery system for vaccine delivery.
Technology Summary: A microneedle patch incorporating silk fibroin-based biomaterials as a controlled-release depot tip on the dissolvable microneedle. The shelf-stable, easy-to-apply, patch enables the adjustable delivery of actives from small molecules to biologics. The needle base dissolves in minutes, embedding the slow-release tips that continue to deliver drugs into the skin for minutes to months.

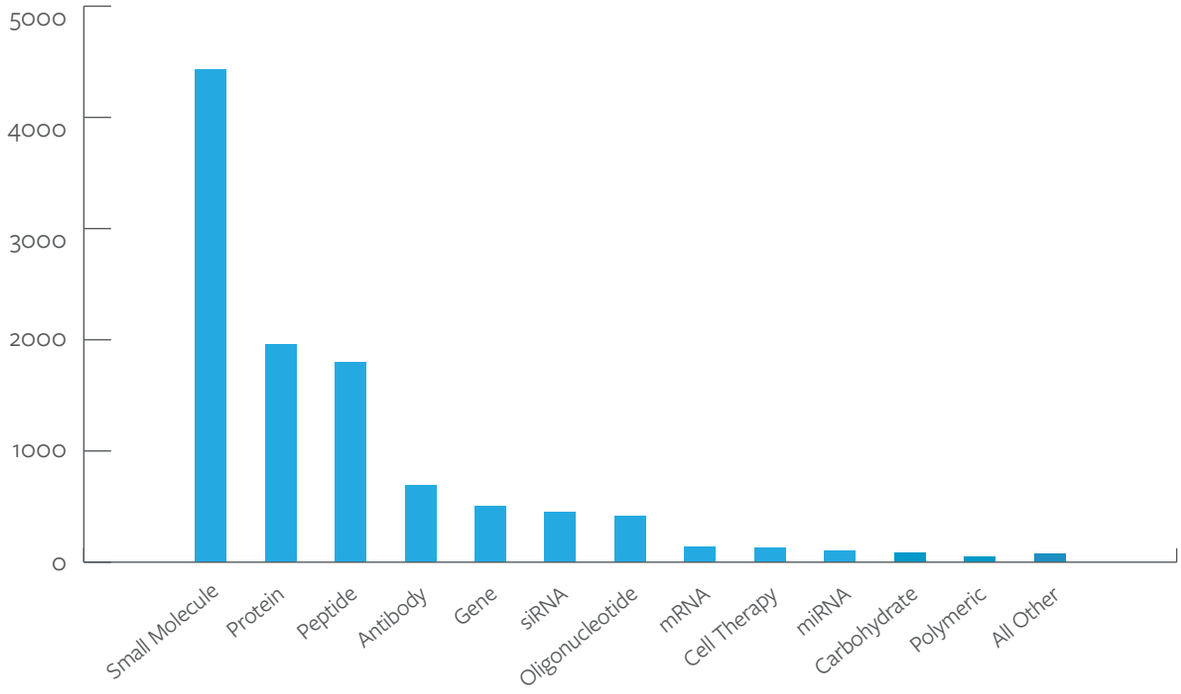
Injection and Small Molecules Continue to Dominate Technology Development Activities

Active Technologies by Delivery Route



Source: PharmaCircle Drug Delivery Technology Analyzer Module March 31, 2021

Active Technologies by Molecule Type



Source: PharmaCircle Drug Delivery Technology Analyzer Module March 31, 2021

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 and Molecule Type. All other includes a variety of technologies and routes not easily assignable to a category.

Drug Delivery and Formulation-Related Transactions Trends of 2020

While there will always be a debate regarding what exactly is drug delivery and formulation in the 21st Century, for this review, we take a broad view of the subject. From this perspective and in the context of where companies put their money in 2020 when it came to technology, there were two obvious areas of investment.

Gene Therapy

Both gene and cell therapy have yet to properly reward the companies that have invested in the platforms, technologies, and products. This may of course just be the calm before the storm that was seen with antibody therapies. An initial sense of optimism in the potential of antibodies that was seen in the late 1980s and early 1990s was largely squashed with a relative lack of meaningful products along with issues related to the humanization of antibodies and identifying therapeutic targets. For the faithful, validation and success arrived shortly thereafter.

Gene and cell therapy had its own moment of enthusiasm in the mid-1990s that was squashed by a fatal reaction to an adenoviral gene therapy. At the same time, the costs of both gene and cell therapy were an order of magnitude greater than what the market was willing to bear. Following a reworking of gene therapy vectors to address safety issues and the evolution of a marketplace that is now willing to accept million-dollar pharmaceutical products, it seems that gene and cell therapy is prepared to explode with a variety of products addressing challenging medical indications. But, after a crop of initial approvals over the past three years, certain realities have started to emerge. This seems to represent the same calm that was seen with antibody therapies. Having learned their lesson, or perhaps being afraid to miss the next wave, many companies chose to invest heavily in both gene and cell therapy in 2020. Some notable transactions include the following:

- 2020-12 Bayer and Asklepios, Alzheimer's, Parkinson's, USD 4 billion
- 2020-10 Roche and Dyno Therapeutics, CNS, Liver, USD 1.8 billion
- 2020-04 Vertex and Affinia, Cystic Fibrosis, CNS, USD 1.6 billion

RNA Therapeutics and Vaccines

The other theme of 2020 was an interest in the foundational technologies necessary to deliver the RNA therapies that captured the world's attention in 2020 with the conditional approvals of the Pfizer/BioNTech and Moderna COVID-19 vaccines. This followed on approvals in 2018, 2019, and 2020 of siRNA therapeutics from Alnylam. With clear evidence that RNA therapeutics are real, there has been renewed interest in accessing the necessary delivery technologies for RNA and oligonucleotides. Notable transactions in 2020 include the following:

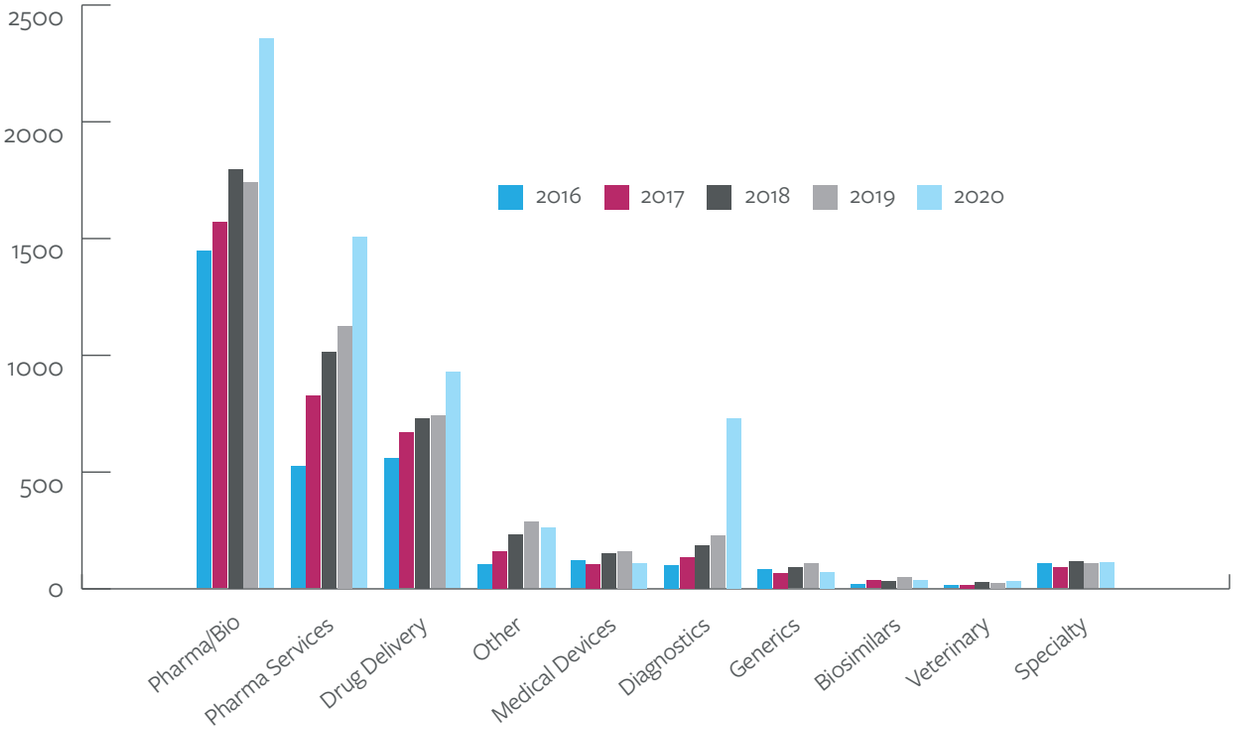
- 2020-06 Sanofi and Translate Bio, Cystic Fibrosis, Infections, USD 1.9 billion
- 2020-01 Ionis and Aro Biotherapeutics, Cancers, USD 1.4 billion
- 2020-06 Lilly and Evox Therapeutics, CNS, USD 1.2 billion
- 2020-09 Chiesi and Moderna, Pulmonary Arterial Hypertension, Cancer, USD 425 million

There were many other drug delivery and formulation-related transactions that included company acquisitions, Gilead and Immunomedics (USD 21 billion), Novo Nordisk and Emisphere (USD 1.4 billion), as well as product and technology acquisitions. Totaled up, these drug delivery and formulation deals exceeded $80 billion in 2020, at least in the usual "Biobuck" currency that always includes performance-related milestone payments.

A focused overview of 2020 transactions by business sector and transaction type are presented in the following charts. In general, transactions experienced a considerable jump in 2020 relative to previous years.

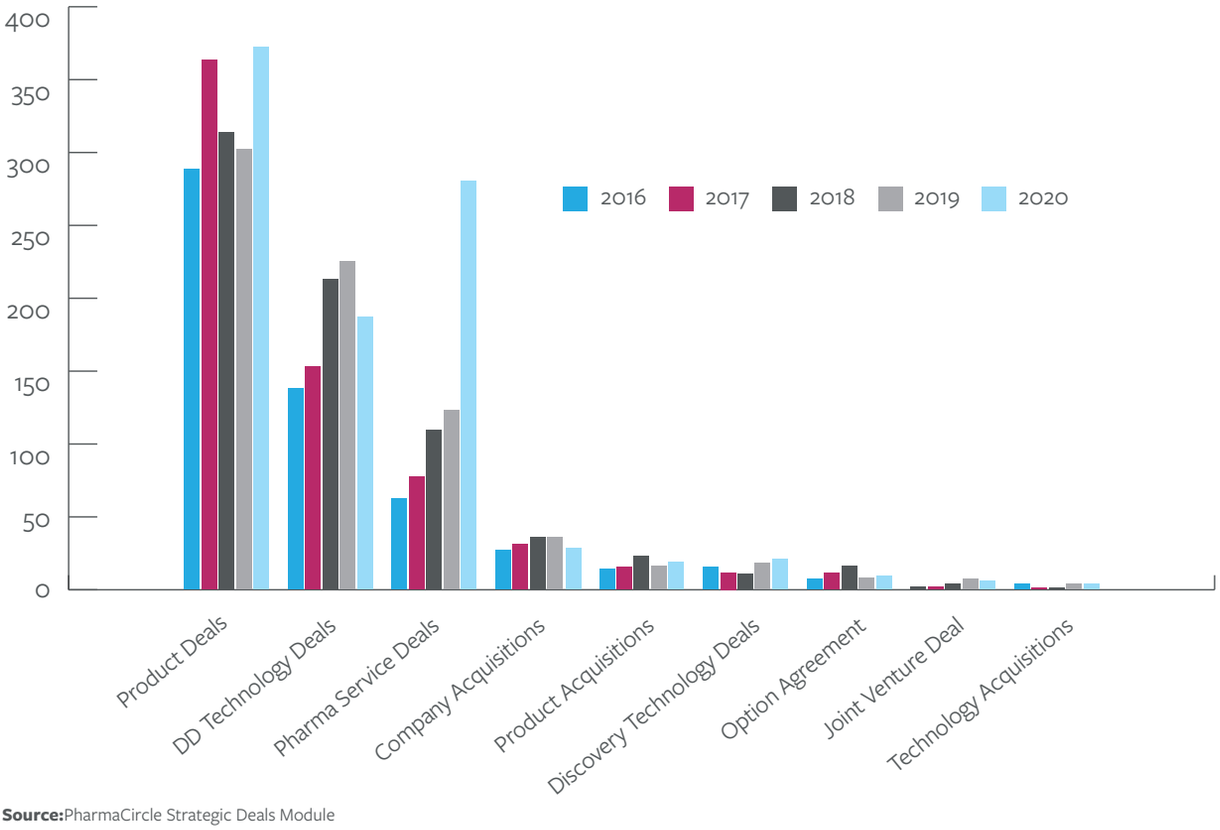
Transactions in the Pharma Sector Jumped Significantly in 2020, Notably Product and Pharma Service Deals

Pharma-Related Transactions by Category (2016-2020)



Source: PharmaCircle Strategic Deals Module

Drug Delivery Transactions by Transaction Type (2016-2020)



Source: PharmaCircle Strategic Deals Module

Table notes: Transaction assignments are made by PharmaCircle analysts. The transaction numbers include amendment and termination agreements which can account for 10%-15% of all transactions.