2019 Global Drug Delivery & Formulation REPORT

Part Four 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

Part 4: The Drug Delivery and Formulation Pipeline

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Introduction

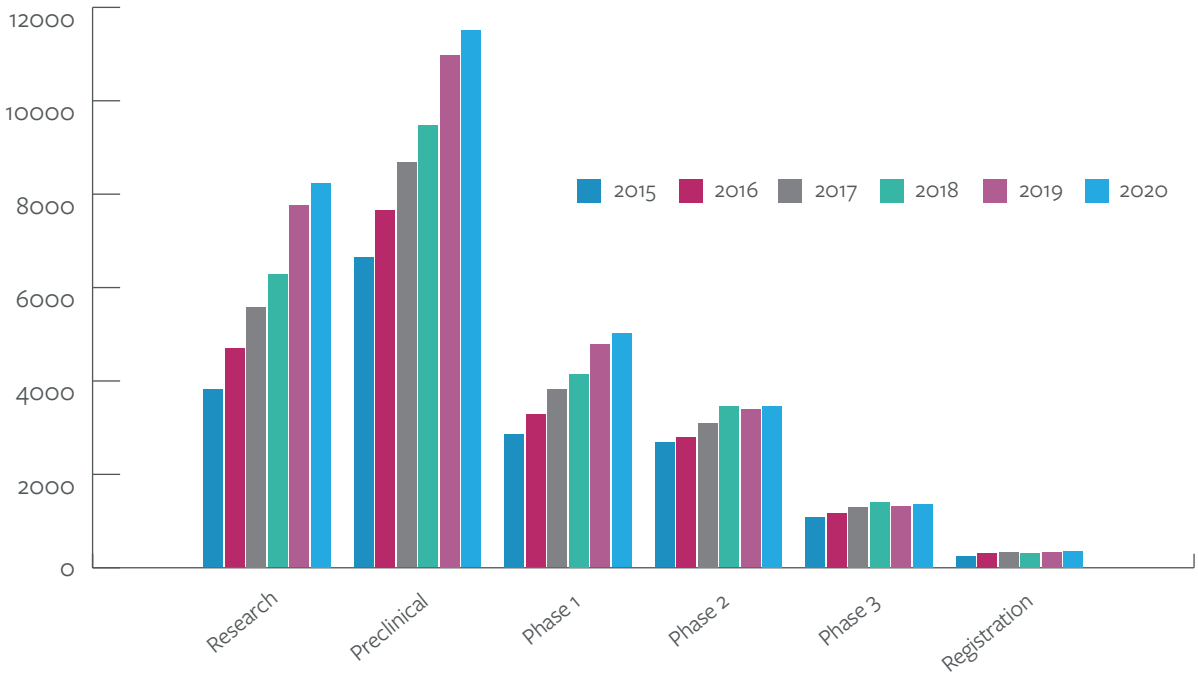
The pharmaceutical industry has certainly seen a major product shift in focus throughout the past decade from large population medical conditions to smaller, orphan type indications. This is exemplified by the US Food and Drug Administration's (FDA) approval of 21 new molecular entity (NME) products in 2019 that had received Orphan Drug designation, representing almost half, 44%, of all NME approvals in 2019. At this point, the FDA has granted 4,352 orphan designations, with 296 alone granted in 2019. There is however much more in the pipeline than orphan products. In fact, the pipeline of products has increased by 65% during the past 5 years, totaling almost 29,000 products and 60,000 programs by early 2020, stretching from Research to Preclinical to Phases 1, 2, and 3 to Registration. This review analyzes the pipeline with an emphasis on clinical-stage products for which there is more product-related information.

The fourth part of this review reinforces the common opinion that cancer therapeutics, often targeted to smaller populations, are receiving increasingly greater investment as expressed in larger numbers of product candidates. It also confirms that more products are being developed using novel molecular scaffolds, typically macromolecules modeled on biological constructs. This new generation of products are not obvious candidates for the majority of the technologies developed and validated for small molecule therapeutics, a suspicion reinforced by an examination of the pipeline in terms of drug delivery and formulation incorporation.

This year's Drug Delivery and Formulation Pipeline analysis uses PharmaCircle's new Pipeline Dynamics companion module to the Pipeline & Products Intelligence module and covers 6 years of pharmaceutical pipeline history. By capturing detailed records annually of what products were at what stage of development from 2015 through to 2020, it is now possible to better understand the dynamic history of product development. The following pages provide a pipeline snapshot according to a number of parameters that are of most interest to drug delivery professionals – Disease Area, Molecule Type, Delivery Route, Product Types, and Drug Delivery Technology Incorporation.

Clinical-Stage Product Growth Has Lagged Behind Preclinical & Research

Pharma Pipeline Product Development, 2015-2020 (Most Advanced Phase)



Source: PharmaCircle Pipeline & Products Intelligence Module (Pipeline Dynamics). Pipeline data as of April 2020.

The booming investment in biopharma is reflected in the steady increase of research and preclinical products in the 5-year period between 2015 and 2020, which has not yet been fully reflected by a similar increase in clinical-stage products. As the number of Phase 1 projects has increased substantially in the 2015 to 2020 period, the growth in the number of Phase 2 and Phase 3 projects has not kept pace. While this may in part be accounted for by changes in clinical trial disclosure requirements that have increasingly led to the disclosure of earlier stage clinical-stage products, it could simply be an issue of companies being more selective in promoting only the very best product candidates to later- stage trials. There may also be a lag effect, reflecting the time required from a first investment in research and preclinical products to produce later-stage clinical candidates. The larger number of Phase 1 products seen in 2020 may well work its way through the system, resulting in a bump of Phase 2 and Phase 3 products in 2022 and beyond.

- The relative distribution of Research/Preclinical/ Phase 1/Phase 2/Phase 3 products in 2020 is 6/8/4/2.5/1. This compares with a 3.5/6/2.5/2.5/1 ratio in 2015.
- Research-stage products increased by 116% over the 2015-2020 period.
- Preclinical-stage products increased by 73% over the 2015-2020 period.
- Phase 1-stage products increased by 75% over the 2015-2020 period.
- Phase 2-stage products increased by 29% over the 2015-2020 period.
- Preclinical-stage products increased by 25% over the 2015-2020 period.

The Movement to Biologic Therapeutics is Most Obvious in the Earliest Clinical-Stage Products

Molecule Type as a Share of All Clinical-Stage Products, 2020

	Phase 1	Phase 2	Phase 3	Registration	All Clinical Stages	% of Total (2015)	% of Total (2020)
Small Molecule	55%	61%	67%	76%	60%	62%	60%
Antibody	12%	10%	10%	7%	11%	9%	11%
Protein	6%	8%	6%	6%	7%	10%	7%
Peptide	5%	6%	6%	5%	6%	7%	6%
Cell & Gene	15%	8%	4%	3%	10%	8%	10%
Oligonucleotide & RNA	2%	2%	1%	1%	2%	2%	2%
Stem Cell	3%	2%	2%	0%	2%	0%	2%
Carbohydrate	1%	1%	2%	1%	1%	1%	1%
All Other	2%	2%	2%	2%	2%	0%	2%

Source: PharmaCircle Pipeline & Products Intelligence Module (Pipeline Dynamics). Pipeline data as of April 2020.

The generally held belief that Biopharma is increasingly investing in more complex biological molecules is reflected in the clinical-stage product pipeline. The Small Molecule product share of all clinical-stage products has dropped from 62% in 2015 to 60% in 2020. This trend is more obvious when one looks at the relative share of Small Molecule products from Phase 1 to Phase 2 to Phase 3 to Registration-stage products, where the Small Molecule share drops from 76% at the Registration stage to only 55% in Phase 1. These proportions are likely to even out a bit more throughout the next few years as the current Phase 1 cohort advances to Phase 2 and Phase 3 trials.

- Protein products seem to be the only molecule type not sharing the general growth in Biologics. The number of clinical-stage Protein products has actually dropped by 4% in the 2015 to 2020 period.
- Cell and Gene Therapy products have seen the largest gain in the 2015 to 2020 period, up 68%, with the largest bump seen at the Phase 1 stage.
- Clinical-stage Antibody products have seen a 58% increase in the 2015 to 2020 period with 909 identified clinical-stage products, 116 of them in Phase 3.
- Stem Cell products present the most surprising increase in clinical-stage products. From no identified clinical-stage products in 2015, the number has grown to 195 products in 2020, with 19 in Phase 3 development.

Cancer & Eye Diseases Have Shown the Greatest Growth Throughout the Past 5 Years

Active Clinical-Stage Programs by Disease Area, 2015-2020

	2015	2020	Change 2015-2020
Cancer	1,642	2,911	77%
Infections	886	1,215	37%
CNS	686	985	44%
Endocrine / Metabolism	519	631	22%
Inflammation / Immune	461	612	33%
Skin Disorders	295	452	53%
Cardiovascular Diseases	306	383	25%
Pain Management	263	324	23%
Respiratory	257	288	12%
Eye Diseases	164	314	91%
All Other	1,103	1,701	54%
Total	6,582	9,816	49%

Source: PharmaCircle Pipeline & Products Intelligence Module (Pipeline Dynamics). Pipeline data as of April 2020. (Note: the figures here represent Programs rather than Products. It is possible for one Product to be in more than one Program in more than one Disease Area.)

Clinical-stage programs have grown almost 50% in the 2015 to 2020 period. The Disease Areas showing above average growth include Cancer (+77%), Eye Diseases (+91%), and Skin Disorders (+53%). The increase in clinical-stage Cancer programs is not really surprising given the significant need, the large number of new disease mechanisms discovered throughout the past decade, and the many new molecular constructs available. More surprising is the large increase in the number of Eye Disease programs at the clinical stage. The overall number of clinical-stage Eye Disease programs is now on par with Cardiovascular, Respiratory, and Pain Management programs. While there continues to be a consensus that Infectious Disease deserves more investment, the growth of the pipeline has dropped relative to the average with increasing contributions from vaccines and reformulations of previously approved actives.

- The Phase 1/Phase 2/Phase 3 distribution of Cancer programs is 1,800/861/255. In 2015, the distribution was 864/571/187 programs, respectively.
- Respiratory represents the greatest laggard in the Top 10 group, up 12%, with 35 Phase 3 programs and a combined 255 programs in Phase 1 and Phase 2.
- Among All Other, only Gastrointestinal (+77%) showed above average growth between 2015 and 2020. The greatest laggards were Genitourinary (+4%) and Male Health (+14%).

Less-Invasive Delivery Routes are Dropping in Favor of Injection

Delivery Route Products as a Share of All Clinical-Stage Products, 2020

	2015	2020	Change 2015-2020
Injection	46%	49%	6%
Oral	40%	39%	-2%
Topical	5%	5%	-7%
Ophthalmic	2%	2%	-7%
Inhalation	3%	2%	-19%
Nasal	2%	2%	-11%
Transdermal	2%	1%	-40%

Source: PharmaCircle Pipeline & Products Intelligence Module (Pipeline Dynamics). Pipeline data as of April 2020. (Note: in the case of early stage clinical programs, notably Phase 1, products often do not provide information regarding Delivery Route. These products are not included in the analysis. While the absolute numbers of products at each stage are as a result somewhat limited, the relative proportions of Delivery Routes for each development stage should be valid, as should the Phase 3 numbers.)

The development of products as a function of Delivery Route for the most part parallels development by Disease Area. Injection, the only Route to show an increase in share, largely owes its increased share to the growing number of treatments for Cancer, an indication often restricted to parenteral routes of delivery. In the opposite sense, the drop in Inhalation as a Delivery Route is consistent with the very limited expansion of Respiratory programs throughout the 2015 to 2020 period. The biggest drop in terms of Delivery Route was with Transdermal delivery. This probably reflects both a relative lack of novel molecules appropriate for transdermal delivery and the commoditization of the many transdermal technology platforms..

- A total of 552 Injection Route products were identified as being in Phase 3 development as of 2020.
- Oral Route still maintains a high prevalence/importance. Increase in Injections is due to both molecules developed (eg, biologics) and disease (eg, Cancer).
- Inhalation, Nasal, and Transdermal had only 27, 20, and 13 products identified as in Phase 3 development.
- Topical Route will always be needed for dermatology-related conditions in which non-invasive delivery is therapeutically feasible.
- Ophthalmic is increasingly focused on improved convenience with better application devices and reduced dosing frequency.

The Clinical Development Pipeline is Less Dependent on New Formulations & Combinations & Drug Delivery in General

Active Clinical-Stage Products by Product Type, 2015-2020

	2015	2020	Change 2015-2020
New Formulation	1,365	1,881	38%
New Combination	245	315	29%
Biobetter	23	16	-30%
All Other	5,233	7,976	52%
All	6,866	10,188	48%

Active Clinical-Stage Products Incorporating Drug Delivery Technology, 2015-2020

	2015	2020	Change 2015-2020
DD Technology	36%	33%	-9%
No DD Technology	64%	67%	5%

Source: PharmaCircle Pipeline & Products Intelligence Module (Pipeline Dynamics). Pipeline data for 2020 is as of April 2020.

Following a heavy emphasis on developing improved formulations of previously approved actives in the 80s, 90s, and 00s, almost all small molecules, the past decade has seen more investment in the development of new molecular entities and products that are not simple formulation enhancements. While the overall 2015 to 2020 growth of clinical-stage products was 48%, New Formulations lagged at a 38% growth. The development of Biobetters, improved versions of previously approved biologics, at no point particularly active, has dropped even further with greater industry interest and emphasis on novel innovative therapeutics. The number of New Combinations has increased in the 2015 to 2020 period although the growth has lagged overall pipeline growth. All Other, the largest group, includes products that do not fall into the New Formulation, New Combination, or Biobetter groups. This group does not include Generics or Biosimilars.

Pipeline products can incorporate drug delivery and formulation technologies as a means to either enable and/or enhance the performance of a pharmaceutical active. The term DD Technology refers to products that incorporate some sort of definable drug delivery or formulation technology. This can mean technologies to enhance the bioavailability of an active, extend the duration of action of a product, or improve stability. Drug Delivery in this context does not include simple oral or injectable components and excipients that do not intentionally impact the pharmacodynamics of a product. The trend seen between 2015 and 2020 with respect to DD Technology is a general drop in its application, from 36% to 33%. The reason may be the general change in pipeline emphasis to biologics, many of which are first-generation products employing basic formulation methods and excipients. It may also reflect the increasing sophistication of small molecule discovery programs leading to product candidates that are optimized structurally with respect to bioavailability and pharmacodynamic properties. You don't need to "add on" if it's already "baked in." This overall trend away from drug delivery and formulation technologies is likely to reverse itself in the next decade as new biologicals are introduced and competitive pressures require companies to differentiate their products using more than simple molecular manipulation.

Final Thoughts

PharmaCircle's Pipeline Dynamics, with 6 years of information, provides a concise summary of what most people already suspected about the evolution of the pharmaceutical pipeline, a greater industry emphasis on Cancer-related products. Obvious, but perhaps a little further back in terms of development, is the increasing number of non-small molecule therapeutics in the clinical-stage pipeline. For those folks who have been looking at how drug delivery and formulation technologies are being applied to new products, the data largely confirms the suspicion that there is more emphasis on molecules not requiring further drug delivery and formulation optimization, and products for which appropriate technologies are not yet available. This latter point suggests an opportunity for future drug delivery technology development. With time, market pressures will encourage companies to look beyond "good enough" to gain a competitive advantage. For many of these new macromolecules, the answer to date has been increasingly sophisticated patient-friendly devices. This is unlikely to suffice when patients can get the same therapeutic benefits with simple once-a-day oral dosing. Novo Nordisk's Rybelsus suggests how this might be accomplished and its success, or lack thereof, will have major ramifications for the development of next-generation technologies.

A common theme of this year's series of reviews has been the relative stasis in drug delivery and formulation deals, technology development, investments, and efforts. This stasis seems to be less an issue of creativity but more of the general lack of technology-focused investments. The consensus "smart money" is currently chasing novel molecules, novel mechanisms, and orphan indications. These are opportunities that will in the near term be increasingly exhausted. What should follow is the optimization of these products through the development of similar, but incrementally enhanced, new molecular entities, or the optimization of the existing and new therapeutics with novel drug delivery and formulation technologies.

Among the hopeful signs in 2019 was the investment in RNA inhibitors. The secret sauce for these new therapeutics largely lies in their efficient and effective delivery. They need to be targeted to the appropriate cellular components with the necessary "permission slips" to gain entrance and avoid the body's defense systems. But don't call this optimization of delivery and targeting Drug Delivery. Drug Delivery is now old, passé, and not worthy of investment. This new stuff, it's much the same in terms of intent if not the technologies, is exciting and worthy of investment.

Appreciate 2019 as a necessary step forward in terms of approvals, pipeline growth, technology development, and improved patient outcomes. Products and pipelines are running ahead of the necessary technologies to support their optimization. The solution for this is more investment. That will come, but it will require business models that are more than the traditional license fee, milestones, and royalties. What is working for this new generation of experimental and risky therapeutics is the promise of acquisition at crazy premiums. It's more immediate than eventual milestones and royalties and keeps the "smart money" happy and ready to invest.

About the Authors

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Kurt Sedo earned his BS in Chemistry and Mathematics from the University of Wisconsin Stevens Point. Prior to joining PharmaCircle in 2003, he held various R&D Scientist positions within Searle/Pharmacia's Pharmaceutical Sciences Department in Analytical Development and Drug Delivery. Mr. Sedo's responsibilities with PharmaCircle include oversight of data integrity, product development, project management, and customer service. In addition to authoring articles, Mr. Sedo regularly presents overviews of the state of drug delivery and formulation at industry conferences.

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