2021 Global Drug Delivery & Formulation REPORT

Part Three of a Three-Part Series

Part 1: A Review of 2021 Product Approvals

Part 2: Notable Drug Delivery and Formulation Product Approvals and Technologies of 2021

Part 3: Drug Delivery and Formulation Pipeline Trends

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Introduction

What immediately pops out when surveying the pharmaceutical product development pipeline is a slowdown in pipeline growth at all stages of clinical and non-clinical development. For products not yet in the clinic, Research and Preclinical, there was a 7% growth rate last year versus an average of 16% to 22% throughout the past 6 years. Clinical-stage annual pipeline growth that averaged 6% to 14% the past 6 years slowed to 3% to 6% this past year. The most obvious reason for the drop in pipeline growth is COVID-19. With companies restricted in terms of operations, and medical institutions focused on treating COVID-19 patients while limiting hospital access, there was little capacity for the initiation of new clinical trials. Even existing trials were slowed down by recruitment issues. This implied that fewer products would be entering the clinic and fewer products transitioning from one stage of development to another.

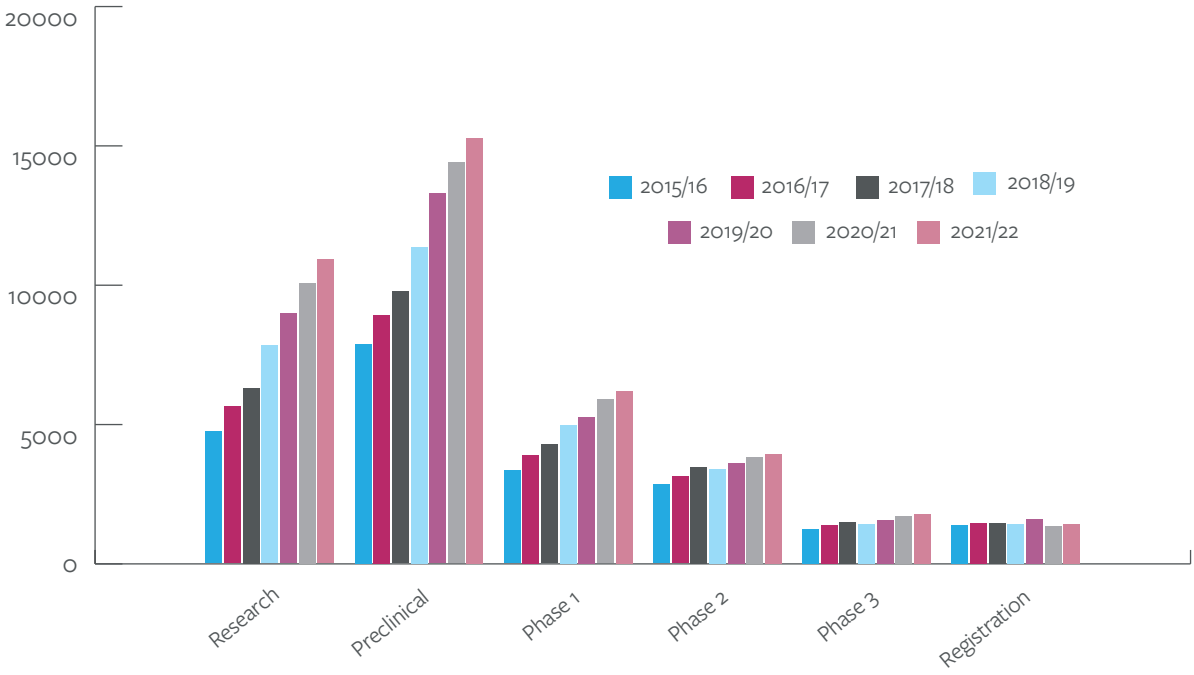
It may also be that companies are showing more discipline with respect to the products they are selecting to enter clinical trials and those they are choosing to advance in the clinic. Several notable product failures in the past year may have also caused companies to pause and rethink their development plans. While a large number of emerging companies received considerable financing, venture and public market, many were not in a position to actually use the funding to advance their programs. It is likely that 2021 will be turn out to be aberration in terms of pipeline growth. Strong funding and the considerable number of medical needs will continue to drive innovation.

Beyond the slowdown in the growth of the pharmaceutical product pipeline, there were few surprises regarding the nature of the pipeline itself. Small molecule therapeutics continued to be the leading molecule type in development this past year, accounting for 59% of all molecule types, although its share continues to shrink. Injection continued to be the favored delivery route in 2021 with a 52% share of all clinical-stage products. Even though small molecules can generally be delivered orally, the large number of cancer and infectious disease products lean on injection routes to optimize efficacy and safety by permitting greater control over administration and distribution.

Whether 2021 was an aberration or the new normal is a question that will be answered over the next few years. The following pages provide additional insights into the nature of the current pipeline in terms of development phase, delivery route, molecule type, and disease area taken from PharmaCircle's Pipeline Dynamics module.

Pipeline growth, from Research through Phase 3, was sharply attenuated in 2021

Pharma Pipeline Product Development, 2015/16 to 2021/22 (Most Advanced Phase)



Source: PharmaCircle Pipeline & Products Intelligence Module (Pipeline Dynamics). The 2021/22 data reflects the pipeline figures for March 31 of the later year, for example, the 2021/22 dataset reflects the pipeline March 31, 2022.

The growth of early stage pharmaceutical products, Research and Preclinical, continues to outpace the growth of clinical-stage products. This is largely accounted for by investor interest in supporting new companies at the ground floor, often with prospects but not yet clinical stage programs. Growth in the past year for Research- and Preclinical-stage products was 8.0% and 6.3%, respectively. This compares with average annual growth rates of 22% and 16% throughout the previous 6 years.

The increase in the Phase 1 (5.8%), Phase 2 (2.5%), and Phase 3 (3.1%) pipelines for the year ending March 31, 2022, fell well short of the 14.3%, 6.6%, and 6.7% average annual growth rates for the previous 6 years.

The reasons for the slowdown in the pipeline growth are many with the most obvious being the negative global impact of COVID-19 on clinical trial initiation. After a flurry of exciting product development announcements throughout the past few years, there was a more sober mood in the past year with a number of high-profile products, often with inflated prospects, failing to deliver expected clinical results.

Small molecule therapeutics remain in the majority but with a shrinking share

Molecule Type as a Share of All Clinical Stage Products, 2021/22

	Phase 1	Phase 2	Phase 3	Share of All Clinical Products (2021/22)	Share of All Clinical Products (2015/16)
Small Molecule	49%	60%	63%	59%	66%
Antibody	14%	11%	14%	12%	9%
Protein	6%	8%	9%	6%	8%
Peptide	5%	6%	5%	5%	6%
Cell & Gene Therapy	16%	6%	4%	10%	8%
Oligonucleotide & RNA	2%	1%	0%	2%	1%
Stem Cell	3%	2%	1%	2%	0%
Carbohydrate	1%	1%	2%	1%	1%
All Other	3%	3%	1%	3%	1%

Source: PharmaCircle Pipeline & Products Intelligence Module (Pipeline Dynamics). The 2021/22 pipeline reflects the pipeline as of March 31, 2021.

The trend toward biologics and macromolecules in the clinic continued in 2021. Throughout the past 6 years, the proportion of small molecule therapeutics in the clinic has dropped from 66% to 49%. Much of this drop can be accounted for by the large number of biologics and macromolecule therapeutics in Phase 1 development. By the time products have reached Phase 3 development, small molecule therapeutics more clearly dominate. The reason could be two-fold, the highly speculative nature of many biological products in early stage clinical development, and/or the development success of dose-modified formulations of existing small molecules, generally later-stage products, targeted to improved clinical benefits or new indications.

The number of cell and gene therapy products in early clinical development continues to surprise. The numbers may well reflect multiple variations of vector and gene constructs being investigated in a variety of indications. The 2021/22 figures are a little bit lower than what was seen with the 2020/21 dataset. The pipeline share of gene and cell therapy products is much lower in later development stages.

For all the excitement surrounding RNA-based therapeutics, these products still represent a small proportion of clinical trial products, on the order of 1 in every 50 products.

The maturity of antibody therapeutics is seen in a consistent share of 11%-14% from Phase 1 through Phase 3. The potential applications and limitations of antibodies are reasonably well understood, which has led to investments in optimizing their presentations, both formulation and device related, to extend their usefulness in the in-patient and out-patient setting.

Cancer continues to be the major focus of pipeline products

Active Clinical Stage Programs by Disease Area, 2015/16 to 2021/22

	2015/16	2021/22	Change	Average Annual Change
Cancer	1,837	3,632	98%	16%
Infectious Disease	996	2,245	125%	21%
CNS	772	1,096	42%	7%
Endocrine/Metabolism	544	663	22%	4%
Inflammation/Immune	538	654	22%	4%
Skin Disorders	361	441	22%	4%
Cardiovascular Diseases	317	370	17%	3%
Pain Management	285	304	7%	1%
Respiratory	255	301	18%	3%
Eye Diseases	192	379	97%	16%
All Other	1,269	1,799	42%	7%
Total	7,366	11,884	61%	10%

Source: PharmaCircle Pipeline & Products Intelligence Module (Pipeline Dynamics). The 2021/22 pipeline reflects the pipeline as of March 31, 2021. (The figures in this table represent programs rather than products. A product may be in development in more than one Disease Area.)

The growth in clinical-stage infectious disease products continues to lead all disease areas, even cancer. The opportunities and needs in infectious disease are driven by new and increasingly resistant viral, bacterial, and fungal targets, best exemplified by COVID-19. While many products may enter the clinic, the attrition rate is very high.

While cancer may have fallen behind infectious diseases in terms of annual growth rate, it stands alone in terms of number of products in clinical development, accounting for 31% of all products. Once again, the needs and opportunities are obvious. What is perhaps unusual is that an increasing number of cancer products in development might well be classified as me-too products pursuing validated therapeutic mechanisms with biologics, often antibodies and small molecules, that struggle to demonstrate meaningful therapeutic improvements. This is an area in which differentiation will depend on providing improved pharmaceutical characteristics possible with drug delivery-, formulation-, and device-based technologies.

The strong growth in the eye diseases clinical pipeline acknowledges the significant expectations of patients and physicians for pharmaceutical solutions to conditions plaguing an increasingly elderly population. The range of products in development include simple reformulations of well-validated actives to provide greater convenience in dosing, through easier patient administration or extended dosing intervals. This is exemplified by products using device-based technologies that can extend dosing intervals of up to 6 months with implants, or as short as a day with drug-releasing contact lenses

The other disease areas show little growth, but that disguises some important new therapeutic treatments for conditions, such as migraine, atopic dermatitis, and asthma, often through unconventional delivery routes.

Clinical stage injectable products continue to take share from other delivery routes

Delivery Route Products as a Share of All Clinical Stage Products, 2021/22

	2015/16	2021/22
Injection	48%	52%
Oral	39%	38%
Topical	6%	4%
Ophthalmic	2%	2%
Inhalation	3%	2%
Nasal	2%	2%
Transdermal	1%	1%

Source: PharmaCircle Pipeline & Products Intelligence Module (Pipeline Dynamics).The 2021/22 pipeline represents the status of the pipeline as of March 31, 2022. (Early stage clinical programs, notably Phase 1, often do not provide information regarding Delivery Route. Products without defined routes are excluded from the analysis.)

There are few surprises with the latest figures regarding delivery route for clinical-stage products. Cancer and infectious diseases treatments that require more precise dosing adjustments according to weight and body area benefit from the flexibility provided by the injection route. In addition, with the increasing number of macromolecule products in development, there is often no option for delivery beyond injection, whether by the subcutaneous, intramuscular, injection, or infusion routes. The availability of many new device and formulation technologies that can simplify dosing by injection in the clinic and out-patient settings make injection a much more palatable dosing option.

The increased use of the injection route is coming at the expense of most delivery routes other than the oral route. For many indications, oral delivery continues to be the preferred dosing route even for indications such as cancer if it can improve the overall patient experience and reduce service delivery costs without compromising efficacy. For example, the approval of an oral tablet formulation of azacitidine, Onureg (Celgene/Bristol Myers Squibb) can simplify out-patient dosing while avoiding outpatient clinic visits. Improved convenience generally leads to better compliance, which leads to better clinical outcomes.

There are interesting new options being developed for delivery by the nasal and ophthalmic routes. These are generally targeted and don't represent a sufficiently large number of products to be visible with a simple analysis as earlier presented. More detail is available at PharmaCircle LLC.