2018 Global Drug Delivery & Formulation REPORT

Four 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

Understanding the pharmaceutical pipeline from the perspective of drug delivery and formulation is tricky. Once you start looking too far into the earlier stage pipeline, you find yourself dealing with incomplete and often undisclosed information. Many of these earlier development products, especially Phase 1 and earlier, are "moonshots" of sorts in which companies are pushing the boundaries of experience in hopes of a breakthrough. For these reasons among others, the pipeline portion of this 2018 Global Drug Delivery & Formulation Report is restricted to products in either Phase 3 or Registration stages of development. These products generally have disclosed indication targets and administration routes, but in some cases, lack details regarding dosage form and formulation.

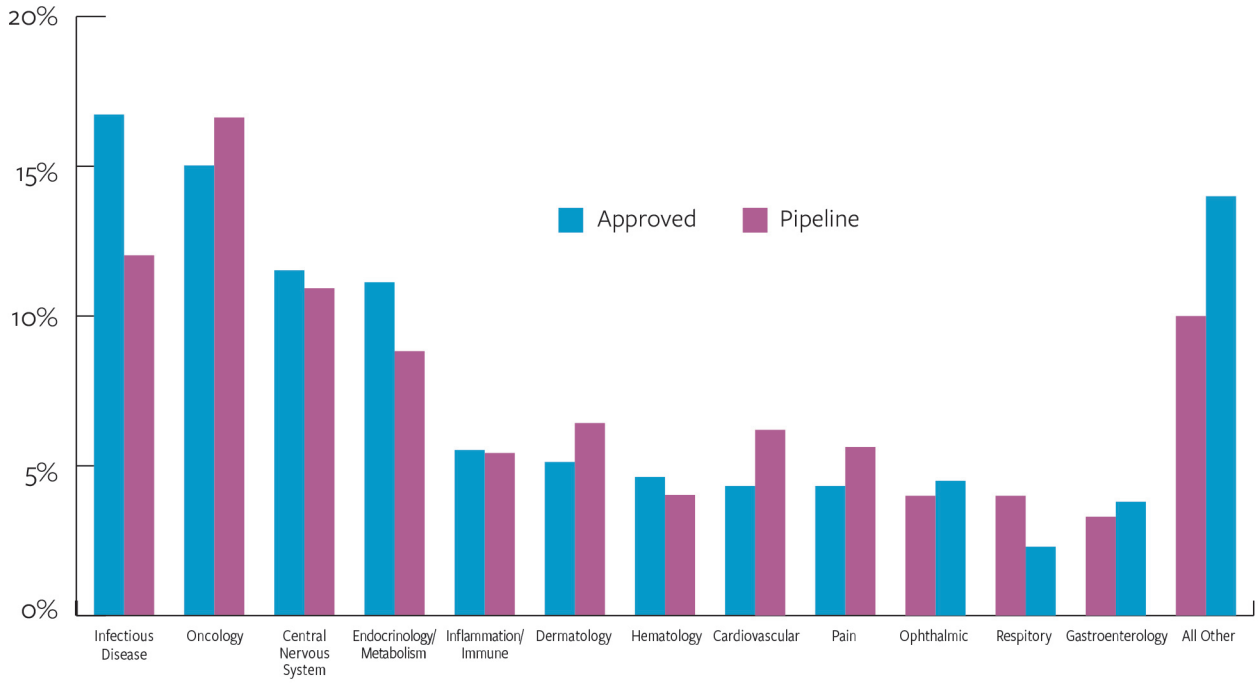
This review compares current Phase 3 and Registration-stage products with products first approved since 2014 in the United States, Japan, or Europe.

The net/net of this analysis, presented over the following pages, reveals more consistency than change in the pipeline products. There are more Oncology products in later stage development, generally targeted antibodies, proteins, and small molecules. This is offset by a drop in the proportion of Infectious Disease agents in development.

The increase emphasis on Oncology and other specific molecular mechanism-targeted therapeutics, often with macromolecules, has resulted in a shift to more Injection-based therapeutics. In terms of molecule types in the pipeline, there is little or no change seen in the ratio of small molecule to macromolecule therapeutics. But among the macromolecules in development, there appears to be an increased proportion of Peptides, was well Gene and Cell Therapy products, at the apparent expense of Protein and Antibody therapeutics.

Oncology is the Leading Indication in the Late-Stage Pipeline

Chart 1: Approved & Product Pipeline by Indication (Top 12)



Source: PharmaCircle Pipeline & Products Intelligence module

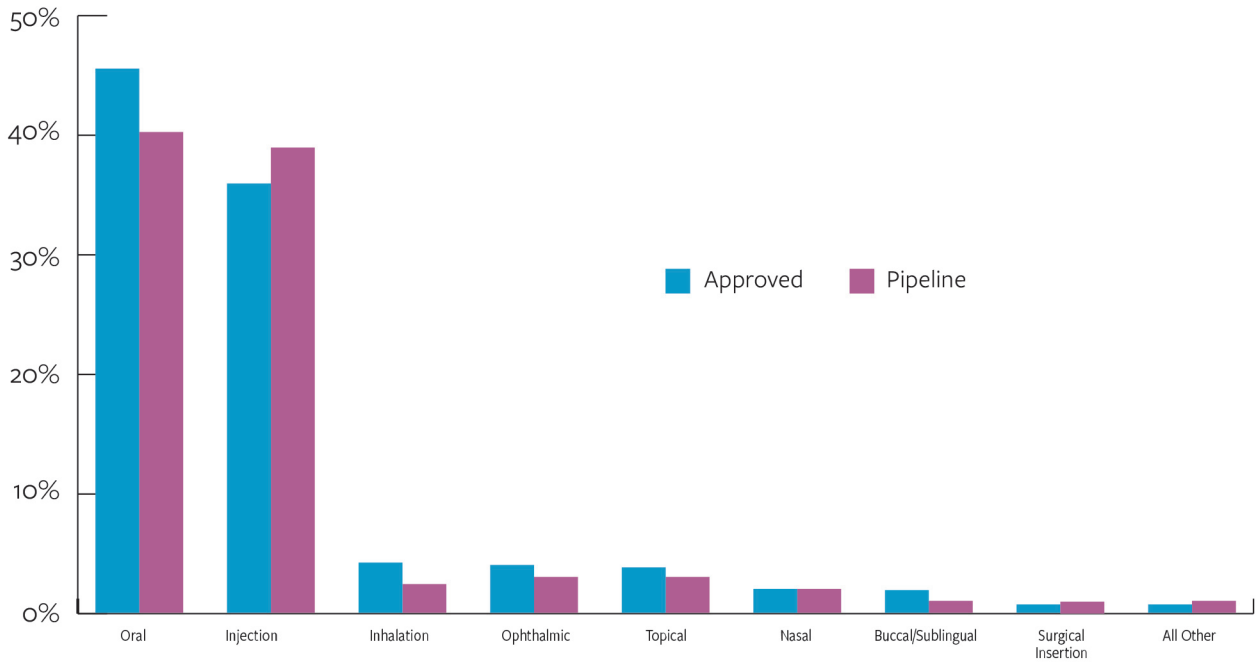
Notes:

1. Approved refers to products with first approvals between 2014 and March 2019 in the US, Europe, or Japan. Generics and Biosimilars are not included. (N=683)
2. Pipeline refers to products identified in Phase 3 or Registration stages of development in major markets as of March 2019. Generics and Biosimilars are not included. (N=1,380)
3. All Other includes Musculoskeletal, Genetic, Genitourinary, Anesthesia, and Men's and Women's Health indications. Each of which represented less than 3% of the total.

- Oncology has moved to the number one development indication, accounting for almost 17% of the late-stage pharmaceutical pipeline.
- The relative drop of the Infectious Disease pipeline is a reflection of a shift away from HIV and HCV after a remarkable string of approvals in the past decade.
- The Cardiovascular market is seeing an increase on the basis of novel therapeutics for more poorly managed conditions, such as Pulmonary Arterial Hypertension.
- The uptick in the Pain sector is not associated with opioids, but rather proprietary formulations of non-opioids as well as novel analgesics.
- The Dermatology pipeline uptick includes a number of new formulations of established actives as well as new systemic products.
- Following a flurry of new Respiratory product approvals related to novel devices, the pipeline has shrunk in relative terms.

The Oral Route is Maintaining a Slim Lead Over Injection in the Late-Stage Pipeline

Chart 2: Approved & Product Pipeline by Route (Top 8)



Source: PharmaCircle Pipeline & Products Intelligence module

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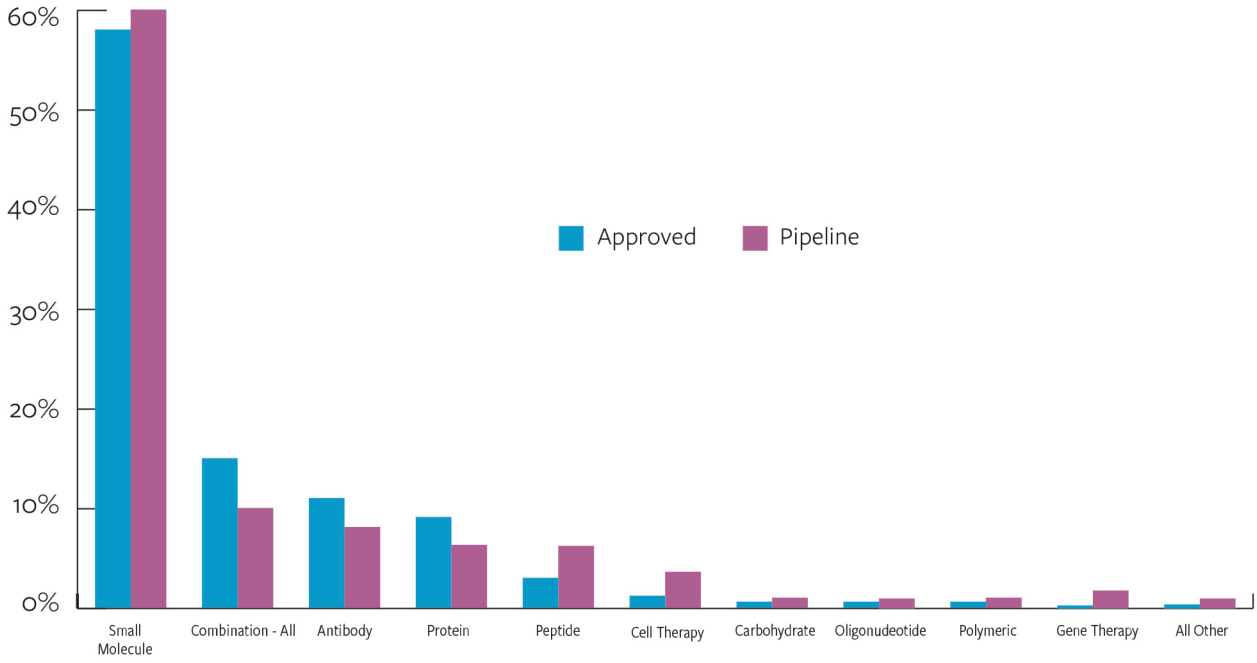
1. Approved refers to products with first approvals between 2014 and March 2019 in either the US, Europe, or Japan. Generics and Biosimilars are not included. (N=693)
2. Pipeline refers to products identified in Phase 3 or Registration stages of development in major markets as of March 2019. Generics and Biosimilars are not included. (N=1,380)
3. All Other includes products delivered by the Otic, Vaginal, Transdermal, or Rectal routes

- The relative drop in the Oral Route seen with the Pipeline products is not surprising in light of an expanded Oncology pipeline largely dependent on parenteral administration.
- The drop in the Inhalation Route pipeline is consistent with the drop in the number of products targeted to Respiratory indications.
- The increase in Topical Route pipeline products parallels the increase in products targeted to Dermatology indications.
- The Buccal and Sublingual routes of administration continue to see little activity in terms of the late-stage pipeline in part a consequence of the relatively poor commercial success of earlier products.
- Transdermal route products, included in All Other, have seen little development interest in terms of the pipeline or recently approved products.
- Nasal delivery continues to see little activity, although newer devices and the potential success of Janssen's Spravato may spur future investments.

Small Molecule Therapeutics Continue to Dominate the Late-Stage Development Pipeline

Chart 3: Approved & Product Pipeline by Molecule Type (Top 10)



Source: PharmaCircle Pipeline & Products Intelligence module

Notes:

1. Approved refers to products with first approvals between 2014 and March 2019 in either the US, Europe, or Japan. Generics and Biosimilars are not included. (N=693)
2. Pipeline refers to products identified in Phase 3 or Registration stages of development in major markets as of March 2019. Generics and Biosimilars are not included. Not all development-stage products have disclosed molecule types, which may impact this analysis. (N=1,247)
3. All Other includes a mix of Plasma-derived, RNA, Stem Cell, and Microbiome products, each with less than a half dozen identified products.

- Small Molecule therapeutics continues to account for more than half of all recently approved and late-stage pipeline products.
- The relative drop in Pipeline antibody products may simply reflect the 10% of Pipeline products that do not have a disclosed molecule type (see Note 2).
- Gene and Cell Therapy products in the late-stage pipeline account for 5.5% of all products, a remarkable leap from 1.5% in the recently approved products.
- The increase in Peptide-based therapeutics from 3% to 6% seems to represent a real trend in terms of the development pipeline.
- The drop in Fixed Dose Combination products is associated with relatively fewer Small Molecule products with two actives.
- Protein-based products showed a bit of a drop in the late-stage pipeline and may be a reflection of incomplete information on these development products (see Note 2).

Oral & Injection Dosage Forms Differ Little Between Approved & Pipeline Products

Chart 4: Approved & Oral Product Pipeline by Dosage Form (Top 4)

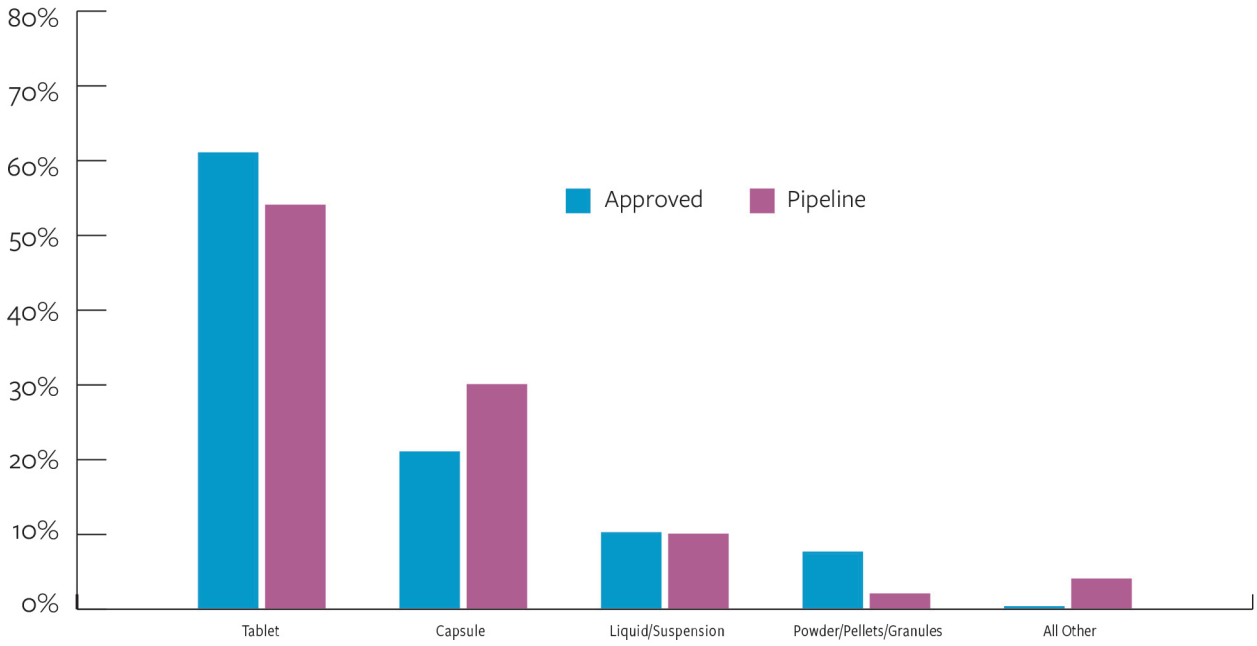
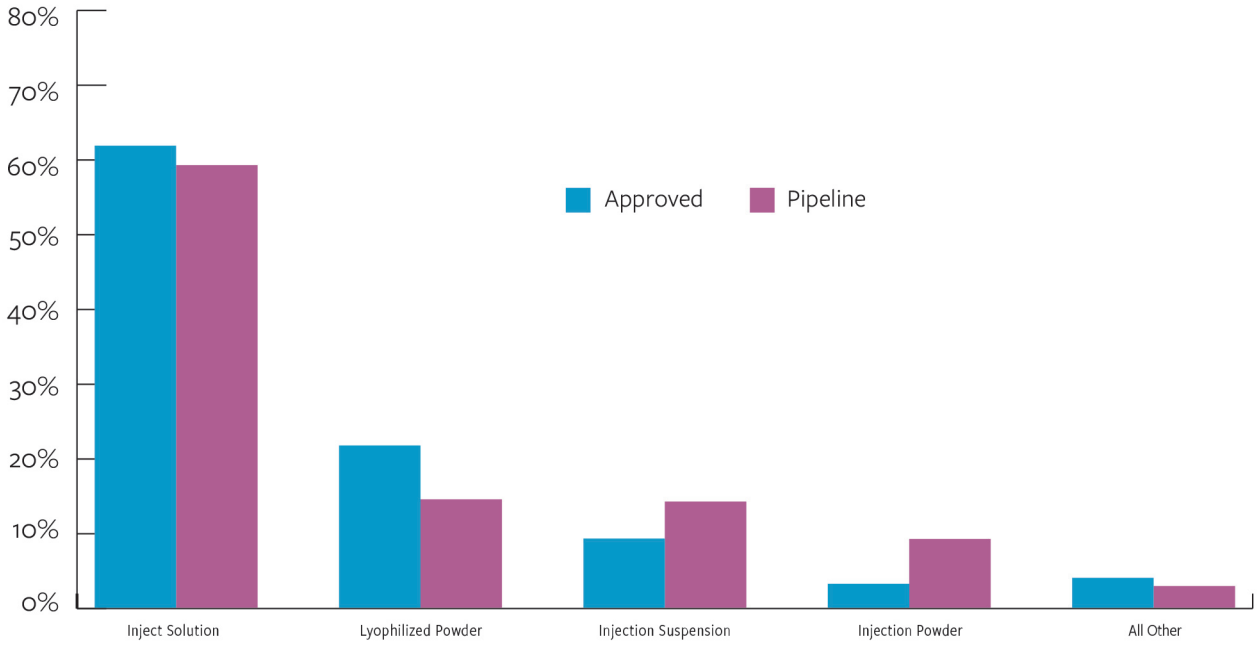


Chart 5: Approved & Injection Product Pipeline by Dosage Form (Top 4)



Source: PharmaCircle Pipeline & Products Intelligence module (both cahrts)

Notes:

1. See earlier charts for definitions of Approved and Pipeline.
2. Oral Approved (N=315). Oral Pipeline (N=499). Injection Approved (N=249). Injection Pipeline (N=380). In many cases, the Pipeline products have undisclosed Dosage Forms.

The Oral & Injection Pipelines Show Consistent Indication Changes

Chart 6: Approved & Oral Product Pipeline by Indication (Top 12)

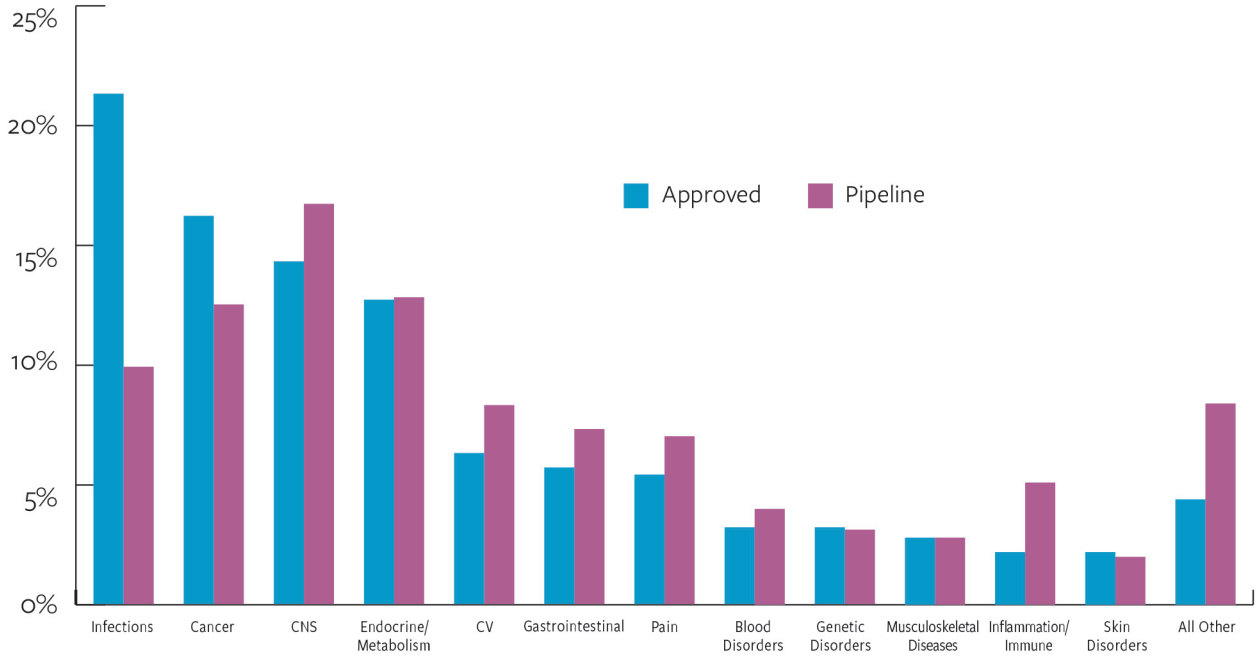
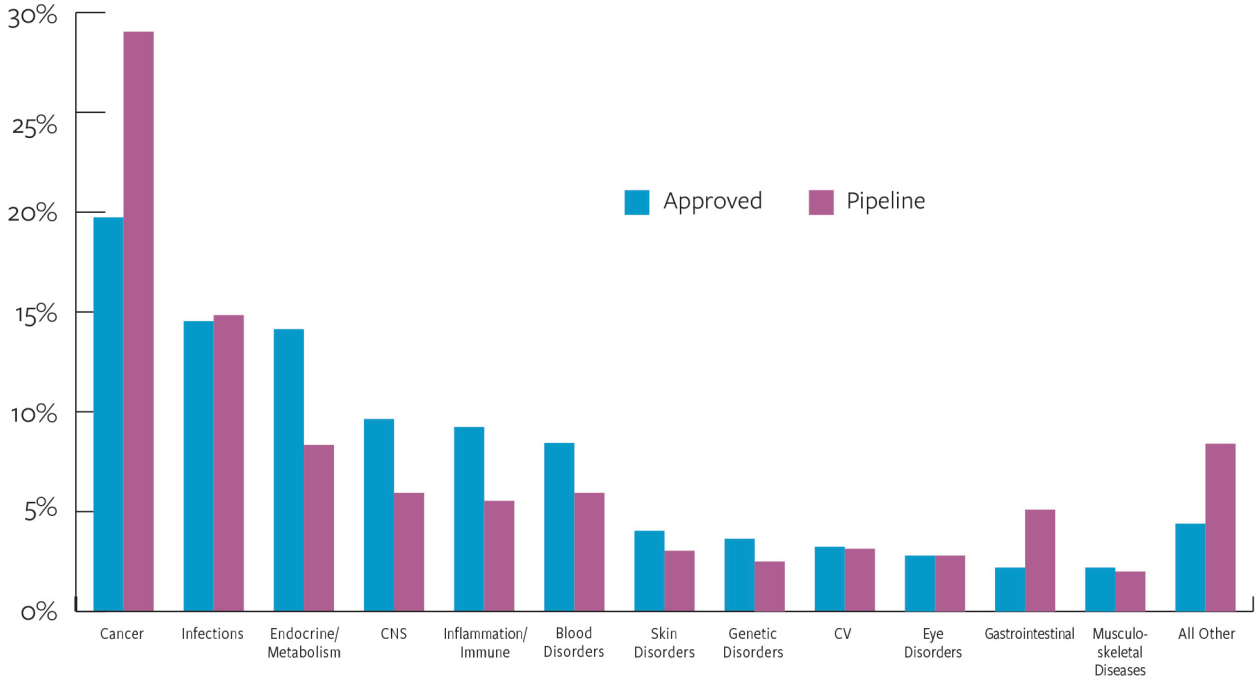


Chart 7: Approved & Injection Product Pipeline by Indication (Top 12)



Source: PharmaCircle Pipeline & Products Intelligence module (both charts)

Notes:

1. See earlier charts for definitions of Approved and Pipeline.
2. Oral Approved (N=315). Oral Pipeline (N=545). Injection Approved (N=249). Injection Pipeline (N=527). In many cases, the Pipeline products have undisclosed Dosage Forms.

Final Thoughts

Looking back at 2018, it's hard to find inflection points in the drug delivery and formulation sector. Looking forward, the late-stage pipeline suggests the future promises more of the same. Should that really be much of a surprise or concern? Do consumer electronics look that much different in 2019 than they did 5 years ago despite much shorter development cycles?

Breakthroughs are needed, and they will arrive. Novo Nordisk's filing earlier this year for approval of an oral formulation of semaglutide, its 4 kDa peptide, using the Emisphere Eligen technology is an important start. The Novo Nordisk filing suggests that oral delivery of larger peptides is effective and safe, although it seems oral dosing requires about 100 times the injectable dose. There is certainly room for improvement. How quickly will 100x be reduced to 20x or even 5x? What's most important is that proof principle has been established. It's no longer a question of whether it can be done, it has become a question of how much better can it become.

The past year experienced more variations on familiar drug delivery and formulation themes; variations on how the technology is deployed, the therapeutic target, and even the therapeutic strategy. In 2018, we saw a number of products approved using quite different PEGylation strategies, multiple smaller PEG units, a single large PEG, and a few mid-size PEG units. They all met different therapeutic objectives for different indications and different molecule types. And the dosing paradigm for ADHD was flipped by 12 hours with the approval of Jornay PM, with an evening dosing using a delayed-release formulation. Familiar but different.

Perhaps the most exciting development was provided by the growing pipeline of gene and cell therapy products that not only address therapeutic challenges with new molecular strategies, but can act as long-term in vivo therapeutic factories. How will drug delivery and formulation contribute? The selective delivery of CRISPR to targeted organs is a real challenge if it is to be used safely for somatic cell applications. Will drug formulators need to take tours of duty through bioengineering departments to expand their skill sets?

The merging of formulation with devices is seeing improved efficacy, safety, and convenience that lead to better healthcare outcomes. When can we expect to see development of the fabled Hypospray from Star Trek, a needleless delivery device with swappable medication vials?

Appreciate 2018 for what it was, another strong step forward for drug delivery and formulation on the path to improved patient outcomes. Inflection points are tricky to recognize, perhaps there were one or more in 2018 that will only be obvious years from now.

About the Authors

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Dr. Kararli earned his PhD in Pharmacology from the University of Florida in 1984 and his MBA from DePaul University in 1999. He worked at Searle/Pharmacia for 18 years with responsibilities in pharmaceutics, product development, drug delivery, and life cycle management. Dr. Kararli founded PharmaCircle in 2003 as a knowledge management organization serving top 20 pharmaceutical companies as well as numerous commercial and emerging-stage life sciences companies and suppliers across the globe. Dr. Kararli has authored numerous research articles on various aspects of pharmaceutics and drug delivery and holds more than a dozen US and international patents.

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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, 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.