2020 Global Drug Delivery & Formulation REPORT

Part One of a Four-Part Series

Part 1: A Review of 2020 Product Approvals

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Introduction

If the Pharmaceutical Industry ever needed a reminder of how important resilience and formulation capabilities were, last year provided convincing evidence. The emergence of COVID-19 has placed a heavy burden on society and the industry. This was particularly evident with the two COVID-19 vaccines that were approved in record time for Emergency Use in the US, BioNTech and Pfizer's Comirnaty and the Moderna COVID-19 Vaccine. While both products reported outstanding clinical results, they have put heavy demands on distribution systems and end-user storage. Comirnaty requires storage at -70°C during transportation and storage. Moderna's vaccine's demands are somewhat less demanding, -20°C, but still strain current infrastructure. These demands are particularly problematic with a need to ship what will eventually be billions of doses.

Formulation should be coming to the rescue as soon as the third quarter of 2021 when it is hoped that lyophilized presentations of both vaccines might be available. There is also a hope that some of the newer vaccines in development, and probably approved for emergency use by the time this article is published, will require only a single dose, cutting transportation issues in half, and perhaps less-stringent temperature management demands.

In the world of Drug Delivery, there were no first products approvals using breakthrough technologies as there was in 2019 with the approval of Novo Nordisk's Rybelsus. Rybelsus was, however, approved in both Europe and Japan in 2020, and its label was expanded in the US. Halozyme's Enhanze technology was also well represented in 2020, with new drug approvals for Janssen's Darzalex FasPro and Genentech's Phesgo, new formulations of previously approved products that provide for the convenience of simple and quick subcutaneous injections rather than hours-long infusions. These two product improvements not only benefit patients and caregivers, but also the companies by quite likely extending their periods of market exclusivity.

Despite all of the challenges of 2020, the regulatory authorities didn't seem to miss a beat. Approvals were at much the same level as 2019. Most, if not all, of the submissions approved in 2020 would have been filed prior to the pandemic, meaning the pressure was on the regulatory authorities to appropriately reconfigure their resources with all of the challenges of social distancing.

What isn't yet apparent is how product development was impacted by the pandemic. Some companies certainly would have had resources reallocated to COVID-19 vaccines and therapeutics development. Social distancing and the application of medical resources to treating COVID-19 patients would have impacted all companies. The FDA also had to deal with restrictions on travel to conduct preapproved inspections.

Looking at the approval data on the following pages it's hard to imagine that the pandemic had any impact on the pharmaceutical industry. Next year's data may tell a different story.

Overall 2020 US NDA and BLA approvals were similar to 2019's numbers

Table 1. FDA Therapeutics Approval Numbers by Classification2 (2019 and 2020)

		2020	2019
BLA (CDER*, CBER*)		**26**	**26**
CDER	Biologic, 351(a) & 351(k)	21	22
	- 351(a) (Innovator)	18	12
	- 351(k) (Biosimilar)	3	10
CBER	Biologic Therapeutics, 351(a)	5	4
NDA (CDER)		**122**	**117**
Type 1	New Molecular Entity	44	39
Type 2	New Active Ingredient	2	7
Type 3	New Dosage Form	25	26
Type 4	New Combination	7	8
Type 5	New Formulation or New Manufacturer	24	32
Type 7	Previously Marketed, Unapproved	0	1
Type 1/4	New Molecular Entity and New Combination	2	1
Type 3/4	New Dosage Form and New Combination	3	0
Other Type	Other Type or Not Specified	11	N/A
Medical Gas	Medical Gas	4	3
ANDA (CDER)	Abbreviated New Drug Approvals (Generic, Multisource)	**903**	**962**

Source: PharmaCircle Pipeline & Products Intelligence and FDA Products Modules

*CDER (Center for Drug Evaluation and Research), CBER (Center for Biologics Evaluation and Research)

- 2020's 26 Biologic approvals, 351(a) and 351(k), matched 2019's total. CBER and CDER Innovative BLA 351(a) approvals, were up almost 50%, while biosimilar 351(k) approvals, dropped by 70%.
- Biosimilar approvals in 2020, 3 in total, fell well short of 2019 (10 approvals) and 2018 (9 approvals).
- 2020's 46 non-biologic novel drug approvals, including single active and combination products, were above the 40 approved in 2019.
- New Dosage Form approvals (Type 3 and Type 3,4) totaled 28, a little ahead of 2019. These products incorporated previously approved actives (PAA), often with the benefit of improved convenience or a focus on pediatric patients.
- New combination approvals incorporating PAA and novel actives totaled 12 in 2020, a bit ahead of 2019 and well short of 20 approvals in 2018.
- New Formulation or New Manufacturer, Type 5, approvals totaled 24 in 2020, well short of 2019's 32, and 2018's 40 approvals.
- There were a large number of products, 11, in 2020 that were not classified by the FDA. This was a mixed bag of approvals that included new presentations with lower sodium content, Xywav, and expanded patient population approvals, as well as a couple of prescription to OTC switches.
- ANDA approvals were down about 6%, with Tentative Approvals representing almost 17% of all ANDA approvals.

Table notes: *Some multisource injectables are approved through the NDA rather than the ANDA regulatory process and can unintentionally skew the new drug approval figures. Type 5 approvals, often injectable multisource products, are not considered in the analyses presented on the following pages.*

Injection Route products continue to represent a significant proportion of new product approvals

Table 2. 2020 Approvals by Administration Route

Route of Administration	**US** (n=132)	**Europe** (n=238)	**Japan** (n=66)
Buccal / Sublingual	1	3	1
Inhalation	2	10	2
Injection (All)	58	83	31
Instillation/Implantation	-	1	-
Nasal	3	-	1
Ophthalmic	4	13	2
Oral	56	97	27
Rectal	-	1	-
Surgical Insertion	2	5	-
Topical	3	17	2
Transdermal	1	1	-
Vaginal	2	4	1

Source: PharmaCircle Pipeline & Products Intelligence module

*CDER (Center for Drug Evaluation and Research), CBER (Center for Biologics Evaluation and Research)

- The approvals in Europe include both EMA and country level approvals for non-generic products. Not surprisingly, products using the Oral route were the most common followed by Injection (All). The Inhalation figures are skewed a little by the EMA practice of granting separate approvals for different brands of the same product. The topical figures are remarkably high in part because of country-level approvals for slightly differentiated formulations using previously approved actives. This is the same reason for the relatively high number of product approvals using the Ophthalmic route.
- The US approval population is consistent with earlier reports and represent new molecular entities and new novel formulations of previously approved actives. With this product set, Injection (All) noses ahead of Oral. Inhalation is an increasingly a less-favored administration route. In some cases, systemic injectables are being developed and approved to treat pulmonary conditions previously treated by inhalation.
- In terms of relative numbers, Japanese product approvals largely parallel the US, with Injection leading Oral.
- Nasal and Transdermal delivery continues to be associated with a very limited number of new approvals. For both Nasal and Transdermal delivery, the issue is largely related to the limited number of molecules suited for what is essentially "transdermal" delivery. The most interesting newer molecules pose increasingly significant demands on all delivery systems by virtue of drug size, limited lipophilicity, and stability challenges.

Table notes: *The figures above include all formulations approved for each product. In a few cases, two or more formulations were approved for a single product. Some products were categorized in two columns, for example, Injection and Ophthalmic, for a product delivered intravitreally. The figures above do not include Type 5 Approvals (FDA), Generics (All), or Biosimilars (All).*

Renewed industry interest in formulation-enhanced products will depend on new technologies

Table 3. 2020 Approvals by Drug Delivery Category

Route of Administration	US (n=132)	Europe (n=238)	Japan (n=66)
Inhalation			
- Devices (Integral*)	1	7	2
- Formulations	1	3	-
Injection			
- Device, Injection Systems (Integral*)	2	13	9
- Device, Pre-Filled Syringes	3	10	4
- Formulations	8	16	6
- Conjugates	13	3	2
- Viral Vectors	-	1	1
- None	29	44	11
Implantation			
- Formulations	-	1	-
Nasal			
- Devices	2	-	-
- Formulations	1	-	-
Ophthalmic			
- Device and/or Pre-Filled Syringes	-	2	-
- Formulation	4	8	1
- None		3	1
Oral			
- Formulations	12	16	6
- None	45	79	20
Topical			
- Formulations	2	4	-
- None	1	11	2
Vaginal			
- Formulations	1	1	1
- None	1	3	-

Source: PharmaCircle Pipeline & Products Intelligence Module

- Good enough seems to be the working approach for most oral products approved in 2020. Formulation-enhanced oral products continue to command a limited share of approvals. With the most obvious oral drug enhancement products already approved, and new molecular entity oral products being approved with optimized pharmaceutical therapeutic and convenience properties, the opportunity for reformulations has dropped. The obvious next formulation advancement, converting chronic therapy injectables to oral dosing, awaits the development of the necessary technology. Novo Nordisk's Rybelsus is but a first step at validating the possibility and potential.
- Injection systems, an increasingly popular option to encourage the use of outpatient injectables, represented a relatively small proportion of total 2020 Injectable approvals. To some extent, this can be attributed to the approval of many new biologic products targeting rare diseases that require only a single injection or infusion, or injections on a monthly or longer interval. For these products outpatient friendly approaches are much less important than efficacy and safety considerations.

Table notes: *The figures above include all formulations approved for each product. In a few cases, two or more formulations were approved for a single product. Some products were categorized in two columns, for example, Injection and Ophthalmic, for a product delivered intravitreally. The figures above do not include Type 5 Approvals (FDA), Generics (All), or Biosimilars (All).*
** - Integral refers to devices that are integrally associated with a product. Examples would include auto-injectors and dry powder inhalers.*

Simple Dosage Forms, Solutions and Tablets, were the norm in 2020

Table 4. 2020 Approvals by Dosage Form

Route of Administration	US (n=132)	Europe (n=238)	Japan (n=66)
Inhalation			
- Inhalation Powder	1	5	2
- Inhalation Suspension	1	4	-
Injection			
- Emulsion	2	1	-
- Gel	-	-	1
- Lyophilized Powder for Solution or Suspension	13	9	5
- Powder for Solution or Suspension	-	4	1
- Solution	37	52	20
- Suspension	5	15	4
Nasal			
- Powder	-	-	1
- Solution	1	-	-
- Spray Solution or Metered	1	-	-
Ophthalmic			
- Implant	2	-	-
- Ointment	-	1	-
- Solution	2	8	-
- Suspension	1	1	1
Oral			
- Buccal or Sublingual	-	3	1
- Capsule	12	17	1
- Capsules, Soft Gel or Liquid Filled	1	5	-
- Film	1	2	-
- Liquid	1	-	-
- Lozenge	-	1	-
- Tablet or Powder for Solution or Suspension	4	3	-
- Sachet, Granules	3	3	2
- Solution	5	8	1
- Suspension	3	1	1
- Syrup	-	3	-
- Tablet	27	54	23
Topical			
- Cream	1	1	-
- Gel	-	3	1
- Lotion	1	-	-
- Ointment	1	1	1
- Patch	-	2	-
- Solution	-	8	-
- Shampoo	-	1	-
- Sponge	1	-	-
- Spray	-	1	-
Other			
- Rectal Suppository	-	1	-
- Transdermal Patch	-	1	-
- Vaginal Insert, Gel, Ring, Suppository or Tablet	-	4	1

Source: PharmaCircle Pipeline & Products Intelligence module

- Dosage Form approvals in 2020 largely paralleled the relatively conservative Route of Administration and Drug Delivery Category approvals with a heavy emphasis on simple Oral Tablet, Oral Capsule, and Injection Solution Dosage Forms.

Table notes: *The figures above include all formulations approved for each product. In a few cases, two or more formulations were approved for a single product. Some products were categorized in two columns, for example, Injection and Ophthalmic, for a product delivered intravitreally. The figures above do not include Type 5 Approvals (FDA), Generics (All), or Biosimilars (All).*

Approvals by Molecule Type in 2020 largely paralleled 2019 approvals

Table 5. 2020 Approvals by Molecule Type

Molecule Type	**US** (n=126)	**Europe** (n=235)	**Japan** (n=66)
Antibody	17	11	6
Carbohydrate	1	4	-
Cell Therapy	1	2	-
Gene Therapy	-	4	1
Natural Product	-	3	-
Oligonucleotide	1	-	1
Peptide	2	5	5
Plasma Derived	-	1	-
Polymeric	-	4	1
Protein	8	17	8
mRNA	2	1	-
SiRNA	1	3	-
Small Molecule	92	178	44
Stem Cell	-	-	-
Vaccine or Virus	1	1	-

Source: PharmaCircle Pipeline & Products Intelligence module

- The US and Japan approval figures best represent the current trend with respect to Molecule Types. The European data includes a number of country-specific approvals that largely represent reformulations of previously approved actives, generally small molecules.
- Macromolecule product approvals, with the exception of Small Molecule and Natural Product approvals, accounted for 27% (34/126) of US approvals, a little bit lower than 2019's 31%. Japanese Macromolecule approvals represented 33% (22/66), a slight drop from 2019's 35% (21/60).
- Both the US and Japan figures are higher in terms of Macromolecule approvals if one considers only new molecular entity approvals. Many of the Small Molecule approvals represent new Dosage Forms and Formulations of previously approved actives targeted to specialty populations, notably pediatric patients.
- Antibody-related approvals in terms of total number were higher in 2020 in all regions, except for Japan where they were flat.

Table notes: *The figures above include all formulations approved for each product. In a few cases, two or more formulations were approved for a single product. Some products were categorized in two columns, for example, Injection and Ophthalmic, for a product delivered intravitreally. The figures above do not include Type 5 Approvals (FDA), Generics (All), or Biosimilars (All).*

References

1. Summary reports of 2020 approvals in all three territories are available at http://www.pharmacircle.com/info.
2. NDA Classification Codes. https://www.fda.gov/media/94381/download.