2021 Global Drug Delivery & Formulation

REPORT

Part One 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

The big question hanging over the pharmaceutical industry and healthcare professionals has been what impact COVID-19 would have on the development and approval of pharmaceutical products. Areas for concern varied widely from how pandemic-related public health restrictions might impact human resources, at the industry, patient, medical infrastructure, regulatory, and supplier levels, and how this might affect productivity. Given the lifecycle of product development and approval, it is likely the real impact of almost two "lost" years will only be revealed in the years to come. Once pivotal clinical trials are completed for a novel pharmaceutical product, a couple of years are required for the preparation of dossiers and review by regulatory bodies, both of which are less likely to be influenced by pandemic restrictions. The larger impact is expected to be related to the conduct of patient trials, particularly those that require regular patient and medical facility availability.

Some sense of the impact on industry productivity is offered by the 2021 FDA new product approval numbers. As suggested earlier, the impact is less likely to be seen in the new molecular entity (NME) products as these products have a longer development cycle and receive a greater sense of urgency from industry and regulatory authorities for commercial and public health reasons. Resources will be allocated by both groups as appropriate to get these products over the finish line. By contrast, products such as new dosage forms and especially new formulations and manufacturers are likely to receive less attention as they bring incremental patient benefits. At the bottom of the list are generic drug approvals. The figures bear this out. While NME approvals by the FDA were up slightly in 2021 versus 2020, generic (ANDA) approvals were down by a third compared with the previous two years. New dosage forms were down a quarter versus the previous year while new formulations were up a little.

The comparable figures for European and Japanese approvals are harder to reliably interpret. The European Medicines Agency (EMA) approvals relate only to specific classes of pharmaceutical products and don't capture the full range of products. The Japanese Pharmaceutical Medical and Medical Devices Agency (PMDA) published approvals are hard to access and properly assess. Taking these considerations into account, neither regulatory jurisdiction saw a drop in 2021 approvals compared with 2020, which might be considered a relatively normal year. The EMA approvals in 2021 were markedly higher than for 2020 and comparable to the 2019 approval numbers. For the European Union and the EMA, the challenge in 2020 was not limited to COVID-19 but also the reorganization and relocation arising from Brexit.

There seemed to be little impact of COVID-19 beyond approval numbers. Longer term trends in terms of dosage form, administration route, and molecule type were largely consistent with the two earlier years. Simple dosage forms continue to be preferred.

Biologics as a group continue to make inroads in terms of new molecular entities leading to a greater number of approved injectable products.

The impact of COVID-19 has not yet squeezed approvals. The pharmaceutical pipeline by development phase will be reviewed in Part 3 and may provide additional insights on what can be expected in the years to come.

Overall US NDA and BLA approvals were down in 2021, most notably generic product approvals

Table 1. FDA Therapeutics Approval Numbers by Classification[2] (2019, 2020, and 2021)

		2021	2020	2019
BLA (CDER*, CBER*)		**31**	**26**	**26**
CDER	Biologic, 351(a) & 351(k)	21	21	22
	- 351(a) (Innovator)	17	18	12
	- 351(k) (Biosimilar)	4	3	10
CBER	Biologic Therapeutics, 351(a)	10	5	4
NDA (CDER)		**111**	**122**	**117**
Type 1	New Molecular Entity	32	44	39
Type 2	New Active Ingredient	6	2	7
Type 3	New Dosage Form	19	25	26
Type 4	New Combination	7	7	8
Type 5	New Formulation or New Manufacturer	38	24	32
Type 7	Previously Marketed, Unapproved	0	0	1
Type 1/4	New Molecular Entity and New Combination	4	2	1
Type 3/4	New Dosage Form and New Combination	1	3	0
Other Type	Other Type or Not Specified	2	11	0
Medical Gas	Medical Gas	2	4	3
ANDA (CDER)	Abbreviated New Drug Approvals (Generic, Multisource)	**627**	**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)

- Total human therapeutic product approvals by the FDA in 2021 were down in all areas except Biologics (BLA). The most notable decrease was seen in New Drug Approvals (NDA), with Generic, New Molecular Entity, and New Formulation approvals all down over 2020 and 2019.
- 2021's 31 Biologic approvals, 351(a) and 351(k), was a step up from 2020 and 2019. The increase was largely accounted for by an increase in CBER vaccines and gene and cell therapies approvals. Only one COVID-19 vaccine or therapeutic, Pfizer/BioNTech's Comirnaty, was among the 2021 BLA approvals.
- Biosimilar approvals in 2021, 4 in total, largely matched the total for 2020 (3) and represented a significant drop from the 10 approvals reported in 2019.
- 2021's 36 non-biologic novel drug approvals, including single active and combination products (Type 1 and Type 1,4), were a notable drop from the previous two years.
- New Dosage Form (Type 3 and Type 3,4) approvals totaled 20 in 2021, another notable drop from the previous two years. These products incorporated previously approved actives (PAA), often with the benefit of improved convenience or a focus on pediatric friendly formulations.
- New Formulation or New Manufacturer, Type 5, approvals bounced back in 2021 to exceed the approval numbers for both 2020 and 2019. These approvals are often associated with injectables, effectively generics that do not qualify for approval through the ANDA process and represent limited novelty.

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.*

Injection route products represent the largest proportion of new product approvals

Table 2. 2021 Approvals by Administration Route

Route of Administration	US (n=170)	Europe (n=258)	Japan (n=82)
Buccal / Sublingual	-	**4** (2%)	-
Inhalation	**2** (1%)	**7** (3%)	**1** (1%)
Injection (All)	**93** (55%)	**93** (36%)	**48** (59%)
Instillation/Implantation/Irrigation	**2** (1%)	**1** (<1%)	**1** (1%)
Nasal	**4** (2%)	**9** (3%)	-
Ophthalmic	**3** (2%)	**20** (8%)	**2** (2%)
Oral	**55** (32%)	**102** (35%)	**26** (32%)
Surgical Insertion	**8** (5%)	**3** (1%)	**1** (1%)
Topical	**2** (1%)	**14** (5%)	**2** (2%)
Transdermal	-	**3** (1%)	**1** (1%)
Vaginal/Intrauterine	**1** (1%)	**2** (1%)	-

Source: PharmaCircle Pipeline & Products Intelligence module

- 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 also underlies 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) significantly outpaces Oral. Inhalation is increasingly becoming a less common administration route for new products with effort being invested in Biologics that address respiratory diseases as common as asthma. In many 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 continue 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 "transcutaneous" delivery, be it mucous or dermal. The most interesting newer molecules pose increasingly significant demands on all delivery systems by virtue of drug size, lipophilicity and stability.

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.*

While intravenous remains dominant, subcutaneous injection is increasingly common

Table 3. 2021 Approvals by Injection Route

Injection Route	US (n=92)	Europe (n=69)	Japan (n=40)
Articular	1%	1%	3%
Intralesional	0%	0%	5%
Intramuscular	14%	13%	10%
Intramuscular, Subcutaneous	5%	1%	0%
Intravenous	39%	38%	38%
Intravenous, Intramuscular	2%	3%	0%
Intravenous, Intramuscular, Subcutaneous	0%	1%	0%
Intravenous, Intraperitoneal	1%	0%	0%
Intravenous, Subcutaneous	12%	9%	0%
Intravitreal	2%	1%	3%
Subcutaneous	20%	32%	43%
Subcutaneous, Intralesional	1%	0%	0%
Suprachoroidal	1%	0%	0%
Tissue	1%	0%	0%

Source: PharmaCircle Pipeline & Products Intelligence module

- There is remarkable consistency among the three territories with respect to the proportion of Injectable approvals in 2021 that used the Intravenous route of administration. Intravenous includes both bolus and infusion administration methods.
- The figures for subcutaneous administration at first glance seem varied, ranging from a high of 43% in Japan to a low of 20% in the US with the EU in the middle. The figures approach parity though when adding in the numbers for subcutaneous being approved as an administration option along with Intravenous and Intramuscular. In total, subcutaneous was the sole or optional administration option for 37% of approved products in the US, 43% in the EU and 43% in Japan.
- Using the same approach of adding together dosing options, dosing by the Intramuscular route was more varied between the territories. Intramuscular administration was approved for 21% of injectable products in the US, 18% in the EU, and 10% in Japan.

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. The figures above do not include Generics (All).*

Simple dosage forms, solutions, and tablets continued to be the norm in 2021

Table 4. 2021 Approvals by Dosage Form

Route of Administration	US (n=177)	Europe (n=247)	Japan (n=82)
Inhalation			
- Inhalation Powder	4	-	-
- Inhalation Solution, Suspension	4	-	1
Injection			
- Emulsion	2	-	-
- Lyophilized Powder for Solution or Suspension	19	10	9
- Solution	59	67	31
- Suspension	14	6	6
- Other	-	5	3
Nasal			
- Spray, Solution or Suspension	4	8	-
Ophthalmic			
- Emulsion	1	-	-
- Solution	2	20	-
Oral			
- Buccal or Sublingual	-	1	-
- Capsule	12	20	6
- Capsules, Soft Gel or Liquid Filled	1	4	2
- Lozenge	-	3	-
- Tablet or Powder for Solution or Suspension	3	3	1
- Sachet, Granules, Pellets	6	3	3
- Solution, Syrup	3	17	2
- Suspension	1	4	-
- Tablet	29	50	12
Topical			
- Cream, Ointment, Solution	2	8	1
- Foam, Gel	-	7	1
- Patch	1	-	-
Other			
- Intrauterine Device	-	2	-
- Implant	2	2	-
- Irrigation Solution	1	-	1
- Rectal Solution	-	1	-
- Stent	6	3	-
- Transdermal Gel, Patch	-	3	2
- Vaginal Gel	1	-	-

Source: PharmaCircle Pipeline & Products Intelligence module

- Simple and familiar dosage forms continued to be the norm for 2021 approvals. The most common injectable dosage form was a simple solution, with or without a dedicated delivery device. Oral dosage forms favored tablets and capsules with additional approvals of products that provided easier to swallow pediatric dosage forms such as granules and pellets. The higher proportion of oral dosage forms in the EU reflects the large number of dose-enhanced and proprietary formulations approved at the country level through the Heads of Medicines (HMA) procedures.

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. The figures above do not include Generics (All).*

Approvals by molecule type in 2021 showed the continuing ascent of biologics

Table 5. 2021 Approvals by Molecule Type

Molecule Type	**US** (n=170)	**Europe** (n=258)	**Japan** (n=81)
Antibody	23 (14%)	27 (10%)	16 (20%)
Antibody / Small Molecule	0	2	0
Carbohydrate	2	3	1
Cell or Gene Therapy	2	2	4
Natural Product	-	4	-
Oligonucleotide	2	-	-
Peptide	16 (9%)	5 (2%)	2 (2%)
Plasma or Tissue Derived	3	3	2
Polymeric	1	1	-
Protein	6 (4%)	11 (4%)	10 (12%)
Protein / Carbohydrate	0	-	1
Protein / Polymer	2	-	-
Small Molecule	108 (64%)	190 (74%)	42 (52%)
Vaccine or Virus	5	10	3

Source: PharmaCircle Pipeline & Products Intelligence module

- The Japan approval figures perhaps best represent the current trend with respect to Molecule Types and new molecular entities. The European data includes country- specific approvals (HMA) that largely represent reformulations of previously approved actives, generally small molecules. The same is somewhat true for the US where many approvals are Type 3 (New Dosage Form) and Type 5 (New Formulation or New Manufacturer), which generally relate to small molecules.
- Most notable perhaps are the inroads that peptides are making in terms of approved products, especially in the US. These molecules provide the eventual potential for non-injectable dosage forms while retaining the specificity of a macromolecule.

***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 Generics (All).*

References

1. Summary reports of 2021 approvals in all three territories are available at http://www.pharmacircle.com
2. NDA Classification Codes. https://www.fda.gov/media/94381/download