Review of Polymorph Patent Application of 30 Small Molecule New Drugs Approved by the FDA in 2023

In 2023, the FDA's Center for Drug Evaluation and Research (CDER) approved a total of 55 new drugs, which included 38 new molecular entities, of which 30 were small molecule drugs. In terms of administration routes and dosage forms among these small molecule drugs, there were 5 liquid formulations (including 2 injections and 3 eye drops), 1 nasal spray, and 24 solid/semi-solid formulations (comprising 23 solid dosage forms and 1 gel), as illustrated in Table 1.

Table 1. Basic information of 38 new molecular entities approved by the FDA in 2023

No.	Brand Name	Active Ingredients	Innovator	Indication	Target	Drug Type	Dosage form
1	Brenzavvy	Bexagliflozin	TheracosBio	Type 2 diabetes mellitus	SGLT-2	Small molecule	Oral solid
2	Jaypirca	Pirtobrutinib	Eli Lilly	Mantle Cell Lymphoma	BTK inhibitor	Small molecule	Oral solid
3	Orserdu	Elacestrant	Stemline Therapeutics	ER+、HER2-、ESR1 mutated advanced or metastatic breast cancer	SERD	Small molecule	Oral solid
4	Jesduvroq	Daprodustat	GSK	Anemia caused by chronic kidney disease for adults on dialysis for at least four months	HIF-PHI inhibitor	Small molecule	Oral solid
5	Filspari	Sparsentan	Travere Therapeutics	Adults with primary immunoglobulin A nephropathy	Endothelin and angiotensin II receptor antagonist	Small molecule	Oral solid
6	Skyclarys	Omaveloxolone	Reata Pharmaceuticals	Friedrich's ataxia	NF E2 related factor 2 stimulants	Small molecule	Oral solid
7	Zavzpret	Zavegepant Hydrochloride	Pfizer	Migraine	CGRP receptor antagonists	Small molecule	Nasal spray
8	Daybue	Trofinetide	Acadia	Rett syndrome	Analogue of the neuropeptide (1-3) IGF-1	Peptide	Oral solution
9	Rezzayo	Rezafungin Acetate	Cidara Therapeutics	Candidemia and invasive candidiasis	Glucan synthase inhibitors	Cyclic Peptide	Injection
10	Joenja	Leniolisib Phosphate	Pharming	Activated phosphoinositide 3-kinase delta	PI3Kδ inhibitor	Small molecule	Oral solid
11	Qalsody	Tofersen	Biogen	Amyotrophic lateral sclerosis in adults who have a SOD1 gene	RNA interference	ASO	Injection
12	Veozah	Fezolinetant	Astellas	Moderate to severe hot flashes caused by menopause	Neurokinin 3 receptor antagonists	Small molecule	Oral solid
13	Miebo	Perfluorohexyloctane	Bausch+Lomb Corp. & Novaliq GmbH	Dry eye disease	Lipid modulators	Small molecule	Eye drops

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No.	Brand Name	Active Ingredients	Innovator	Indication	Target	Drug Type	Dosage form
14	Xacduro	Sulbactam, Durlobactam	Innoviva	Hospital-acquired bacterial pneumonia and ventilator-asso-ciated bacterial pneumonia	β-lactamase inhibitor	Small molecule	Injection
15	Posluma	Flotufolastat F-18 Gallium	Blue Earth Diagnostics	Use with positron emission tomography imaging in certain patients with prostate cancer	Target PSMA	Peptidomimetics	Injection
16	Paxlovid	Nirmatrelvir, Ritonavir	Pfizer	Mild-to-moderate COVID-19 in adults at high risk for progression to severe	3C protease inhibitor, CYP3A4 protease inhibitor	Small molecule	Oral solid
17	Inpefa	Sotagliflozin	Lexicon	Heart failure	SGLT-1/2 inhibitor	Small molecule	Oral solid
18	Litfulo	Ritlecitinib Tosylate	Pfizer	Severely patchy hair loss	JAK3 inhibitor, TEC inhibitor	Small molecule	Oral solid
19	Vanflyta	Quizartinib Dihydrochloride	Daiichi Sankyo	As part of a treatment regimen for newly diagnosed acute myeloid leukemia that meets certain criteria	FLT3 inhibitor	Small molecule	Oral solid
20	Xdemvy	Lotilaner	Tarsus	Demodex blepharitis	GABA-A receptor antagonists	Small molecule	Eye drops
21	Izervay	Avacincaptad Pegol Sodium	Iveric Bio	Geographic atrophy secondary to age-related macular degeneration	Complement C5 inhibitor	Small molecule	Eye drops
22	Zurzuvae	Zuranolone	Biogen&Sage Therapeutics	Postpartum depression	GABA A receptor positive allosteric modulator	Small molecule	Oral solid
23	Aphexda	Motixafortide Acetate	BioLineRx	Multiple myeloma	CXCR4 inhibitor	Cyclic peptide	Injection
24	Sohonos	Palovarotene	Ipsen	Reduce the volume of new heterotopic ossification in adults and pediatric patients with fibrodysplasia ossificans progressiva	Retinoic acid receptor gamma agonist	Small molecule	Oral solid
25	Ojjaara	Momelotinib Dihydrochloride	GSK	Intermediate or high-risk myelofibrosis in adults with anemia	JAK1/JAK2/ALK2 inhibitor	Small molecule	Oral solid
26	Exxua	Gepirone Hydrochloride	Fabre-Kramer Pharmaceuticals	Major depressive disorder	5-HT1A serotonin receptor agonist	Small molecule	Oral solid
27	Rivfloza	Nedosiran Sodium	NovoNordisk	Patients 9 years and older with primary hyperoxaluria type 1	ASGR1&L-lactate dehydrogenase inhibitor	siRNA	Injection
28	Velsipity	Etrasimod Arginine	Pfizer	Moderately to severely active ulcerative colitis in adults	Sphingosine 1 phosphate receptor modulator	Small molecule	Oral solid
29	Zilbrysq	Zilucoplan Sodium	UCB	Generalized myasthenia gravis in adults who are anti-acetylcholine receptor (AChR) antibody positive	Complement C5 inhibitor	Cyclic peptide	Injection
30	Agamree	Vamorolone	Santhera Pharmaceuticals& ReveraGen BioPharma	Duchenne muscular dystrophy	Glucocorticoid receptor agonist	Small molecule	Oral solid
31	Fruzaqla	Fruquintinib	Hutchmed&Takeda	Refractory, metastatic colorectal cancer	EGFR	Small molecule	Oral solid
32	Defencath	Heparin Sodium, Taurolidine	CorMedix	Reduce the incidence of catheter-re-lated bloodstream infections in adults with kidney failure receiving chronic hemodialysis through a central venous catheter	AT III agonist, LPS inhibitor	Small molecule	Injection
33	Augtyro	Repotrectinib	BMS	ROS1-positive non-small cell lung cancer	ROS1/TRK/ALK protein inhibitor	Small molecule	Oral solid
34	Truqap	Capivasertib	AstraZeneca	HR+、HER2- breast cancer	AKT inhibitor	Small molecule	Oral solid

Table 1. Basic information of 38 new molecular entities approved by the FDA in 2023

No.	Brand Name	Active Ingredients	Innovator	Indication	Target	Drug Type	Dosage form
35	Ogsiveo	Nirogacestat Hydrobromide	SpringWorks Therapeutics	Adults with progressing desmoid tumors who require systemic treatment	A γ-secretase inhibitor	Small molecule	Oral solid
36	Fabhalta	Iptacopan Hydrochloride	Novartis	Paroxysmal nocturnal hemoglobinuria	Factor B inhibitor	Small molecule	Oral solid
37	Filsuvez	Birch Triterpenes	Amryt	Wounds associated with dystrophic and junctional epidermolysis bullosa	N/A	Small molecule	Gel
38	Wainua	Eplontersen	AstraZeneca & Ionis	Polyneuropathy of hereditary transthyretin-mediated amyloidosis	TTR inhibitor	ASO	Injection

The review of polymorph patent fillings for the 24 solid or semi-solid small molecule new drugs revealed that polymorph patents had been applied for in 20 cases, representing 83% of the total solid or semi-solid small molecule new drugs. Refer to Table 2 for detailed information.

Tablet 2. Basic information and polymorph patent information of 24 small molecule new drugs for solid/semi-solid preparations

No.	Brand Name	Active Ingredients	Innovator	Polymorph patent status
1	Brenzavvy	Bexagliflozin	TheracosBio	Granted
2	Jaypirca	Pirtobrutinib	Eli Lilly	Partial granted
3	Orserdu	Elacestrant	Stemline Therapeutics	Granted
4	Jesduvroq	Daprodustat	GSK	Granted
5	Filspari	Sparsentan	Travere Therapeutics	Under examination
6	Skyclarys	Omaveloxolone	Reata Pharmaceuticals	Granted
7	Joenja	Leniolisib Phosphate	Pharming	Withdrawn (crystal forms disclosed in compound patent)
8	Veozah	Fezolinetant	Astellas	Withdrawn
9	Paxlovid	Nirmatrelvir,Ritonavir	Pfizer	Granted (crystal forms disclosed in compound patent)
10	Inpefa	Sotagliflozin	Lexicon	Granted
11	Litfulo	Ritlecitinib Tosylate	Pfizer	Partial granted
12	Vanflyta	Quizartinib Dihydrochloride	Daiichi Sankyo	Granted

Tablet 2. Basic information and polymorph patent information of 24 small molecule new drugs for solid/semi-solid preparations

No.	Brand Name	Active Ingredients	Innovator	Polymorph patent status
13	Zurzuvae	Zuranolone	Biogen&Sage Therapeutics	Granted
14	Sohonos	Palovarotene	Ipsen	Not found
15	Ojjaara	Momelotinib Dihydrochloride	GSK	Granted
16	Exxua	Gepirone Hydrochloride	Fabre-Kramer Pharmaceuticals	Not found
17	Velsipity	Etrasimod Arginine	Pfizer	Granted
18	Agamree	Vamorolone	Santhera Pharmaceuticals & ReveraGen BioPharma	Granted
19	Fruzaqla	Fruquintinib	Hutchmed&Takeda	Granted
20	Augtyro	Repotrectinib	BMS	Granted
21	Truqap	Capivasertib	AstraZeneca	Granted
22	Ogsiveo	Nirogacestat Hydrobromide	SpringWorks Therapeutics	Granted
23	Fabhalta	Iptacopan Hydrochloride	Novartis	Granted
24	Filsuvez	Birch Triterpenes	Amryt	Not found

Table 3 provides a detailed analysis of the expiration dates for both compound patents and polymorph patents for these 20 drugs, along with the time gaps between them. It was found that 15 of these drugs have polymorph patents expiring later than their compound patents, with a gap exceeding 1 year. Specifically, 11 drugs show a time difference of 3 or more years, 8 drugs have a gap of 5 or more years, and notably, three drugs (Orserdu, Agamree and Ogsiveo) exhibit a time difference of over 10 years.

Table 3. Analysis of Compound Patents and Polymorph Patents for 20 Small Molecule New Drugs

No.	Brand Name	Compound patent	Expiration date[2]	Polymorph patent	Expiration date[3]	Time gap[4] (Month)
1	Brenzavvy	US7838499B2	2029/1/30	US8987323B2	2032/5/14	~45
2	Jaypirca	US10695323B2	2036/12/16	US20210330643A1	Filing date 2019/07/29	N/A
3	Orserdu	US7612114B2	2026/08/18	US11643385B2	2039/7/3	~155
4	Jesduvroq	US8324208B2	2028/12/11	US11117871B2	2038/3/13	~111
5	Filspari	US6835741B2	Expired	US20220048900A1	Filing date 2019/12/20	N/A
6	Skyclarys	US8124799B2	2029/12/3	US8993640B2	2033/4/24	~40
7	Joenja	US8653092B2	2032/2/19	US20180265509A1	Filing date 2011/7/1	N/A
8	Paxlovid	US11351149B2	2041/8/5	US11351149B2	2041/8/5	N/A
9	Inpefa	US8476413B2	2028/5/29	US8217156B2	2030/10/7	~28
10	Litfulo	US9617258B2	2034/12/3	US20210387989A1	Filing date 2019/10/21	N/A
11	Vanflyta	US7820657B2	2028/9/26	US8883783B2	2031/7/12	~34
12	Zurzuvae	US9512165B2	2034/4/17	US11236121B2	2037/8/23	~40
13	Ojjaara	US8486941B2	2030/1/3	US9469613B2	2035/6/11	~65
14	Velsipity	US8580841B2	2030/3/5	US10301262B2	2036/6/21	~75
15	Agamree	US3947409A	Expired	US11382922B2	2040/7/16	>198
16	Fruzaqla	US7829574B2	2028/5/9	US10519142B2	2035/9/7	~88
17	Augtyro	US9714258B2	2035/1/23	US10294242B2	2036/7/5	~17
18	Truqap	US8101623B2	2030/3/10	US9487525B2	2033/4/16	~33
19	Ogsiveo	US7342118B2	2025/8/18	US10941118B2	2039/8/9	~168
20	Fabhalta	US9682968B2	2034/7/14	US11603363B2	2041/5/25	~82

To provide a clearer insight into how innovator companies extend the lifecycles of their products using polymorph patent layouts, we will delve into three representative drugs: Skyclarys, Zurzuvae, Ogsiveo. The authorization of these drugs represents crucial breakthroughs in the treatment of their respective diseases. Additionally, their market share projections highlight their potential to become blockbuster drugs.

Skyclarys

Skyclarys (Omaveloxolone) is a drug developed by Reata Pharmaceuticals, a medication approved for the treatment of Friedreich ataxia (FA), a progressive neurodegenerative disorder, in adults and adolescents aged 16 and older. It stands as the sole FDA-approved treatment for this specific condition. Omaveloxolone's effectiveness is attributed to its dual action: activating the antioxidative transcription factor Nrf2 and inhibiting the pro-inflammatory transcription factor NF-κB. On February 28, 2023, Reata Pharmaceuticals announced the FDA's approval for Skyclarys, presenting a new avenue for potentially alleviating disease progression in Friedreich ataxia patients.

In the commercialized version of the drug, the active ingredient is the crystalline form of Omaveloxolone. The original compound patent (US8124799B2) for this is set to expire on December 3, 2029. Meanwhile, the polymorph patent (US8993640B2), which covers various amorphous and solvent form/hydrates of Omaveloxolone, will expire later on April 24, 2033. The application of the polymorph patent effectively extends the product's protection by about 40 months.

Zurzuvae

Zurzuvae (Zuranolone), an oral medication developed by Biogen and Sage Therapeutics, is designed to treat postpartum depression (PPD), a prevalent complication affecting 15%-30% of women during and after pregnancy. Unlike existing antidepressants that often take time to show significant effects, Zurzuvae stands out with its rapid efficacy. It functions as a positive allosteric modulator of γ-aminobutyric acid A (GABAA) receptors and is noted for its high oral bioavailability and affordability. Biogen and Sage Therapeutics received FDA approval for Zurzuvae on August 4, 2023, offering a swift and effective treatment option for those suffering PPD symptoms.

The marketed form of Zurzuvae contains Zuranolone in its crystalline state. Its compound patent (US9512165B2) is set to expire on April 17, 2034. Additionally, the polymorph patent (US11236121B2), which details a range of Zuranolone polymorphs from type A to type P, including anhydrous forms, hydrates, and solvates, will expire on August 23, 2037. By applying the polymorph patent, the protection duration of the product has been effectively extended by around 40 months.

Ogsiveo

SpringWorks Therapeutics developed Ogsiveo (Nirogacestat Hydrobromide), the first oral tablet for treating desmoid tumors in adult patients. Nirogacestat is a selective inhibitor targeting the gamma secretase (GS) enzyme. It works by binding to GS, which prevents the proteolytic activation of Notch receptors. This inhibition of Notch signaling pathway may lead to apotosis in tumor cells that exhibit excessive Noth expression. On November 28, 2023, SpringWorks Therapeutics announced FDA approval for Ogsiveo, marking it as a treatment option for systemic management of progressive fibrous dysplasia in adults.

The active ingredient in the commercial version of Ogsiveo is the crystalline form of Nirogacestat Hydrobromide. The primary compound patent for Ogsiveo (US7342118B2) will expire on August 18, 2025. Meanwhile, the polymorph patent (US10941118B2), which discloses various forms of Nirogacestat Hydrobromide polymorphs ranging from type A to type N, is due to expire on August 9, 2039. Importantly, the implementation of the polymorph patent has resulted in extending the product's protection by approximately 14 years.

Summary

An examination of data from the last six years (as detailed in Table 4) shows that aside from 2022, the FDA has consistently approved 40 to 60 new drugs annually, with 30 to 40 of these being small molecule new drugs, and 20 to 30 being small molecule oral solid formulations. Despite various challenges faced by the pharmaceutical industry these years, there was a significant increase in the number of approved new drugs last year, reaching levels comparable to the peak observed between 2018 and 2020. It is noteworthy that in the first five years, the rate of polymorph patent applications for small molecule drugs in solid or semi-solid formulations remained steady at 60% to 70%. However, this year saw a rise to 83%, indicating a growing focus on the research of drug solid-state and the application of polymorph patents.

Table 4. Summary of new drugs approved by FDA in the last 6 years

Year	2018	2019	2020	2021	2022	2023
New drugs approved by FDA	59	48	53	50	37	55
Small molecule new drugs	39	32	34	31	17	38
Solid/Semi-solid formulations drugs	31	26	20	23	15	24
Drugs with polymorph patent application	19	17	12	16	10	20
Proportion	61%	65%	60%	70%	67%	83%

The focus on drug crystal forms and the application of polymorph patents has increasingly become a critical aspect for innovator companies in the development of new drugs. This heightened attention stems from two main factors. Firstly, the crystal forms of a drug plays a vital role in its stability, the feasibility of its process development, and its bioavailability. These aspects are crucial in the new drug development and are key considerations for regulatory authorities when approving small molecule drugs. Secondly, securing effective patent protection for drug crystal forms creates substantial technological barriers, allowing innovator companies to fend off competition from generic manufacturers. This strategy extends the market protection duration for new drugs and leads to greater economic benefits. Hence, research on drug crystal forms and strategic application of polymorph patents holds significant importance for innovator companies.

For many year, Crystal Pharmatech has been extensively engaged in the polymorphic research of small molecule drug. The company offers a range of services in drug solid-state research and development, including crystal screening and developability assessment. Additionally, Crystal Pharmatech specializes in providing various services related to the application and analysis of polymorph patents, which are customized to meet diverse drug research and development requirements, as detailed in Table 5.

Table 5. Services related to Polymorph patent

Drug development stage	Polymorph patent strategy analysis	Patentability assessment	Polymorph patent application research scheme	Polymorph patent application	Patent reply support	Formulation of non-infringement strategy	Formulation of defense strategy
Pre-Tox	√	√	√	√			
Pre-IND	√	√	√	√			
Phase I	√	√	√	√			
Phase II	√	√	√	√	√	√	√
Phase III	√	√	√	√	√	√	√
NDA	√	√	√	√	√	√	√
Post Marketing	√	√	√	√	√	√	√

References

[1] https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2023.
[2] https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm.
[3] For granted patents, the official expiration date as announced is considered authoritative.
[4] Expiration date of the polymorph patent minus the expiration date of the compound patent.