



U.S. FOOD & DRUG
ADMINISTRATION

Trends in Designation and Approvals of Drugs for Rare Diseases and Conditions

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December 5, 2023

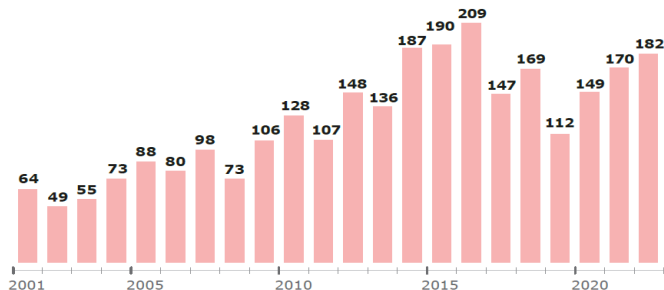
Committee on Processes to Evaluate the Safety and Efficacy of Drugs for Rare Diseases in the
United States and the European Union

over **2730** medicines with orphan designation

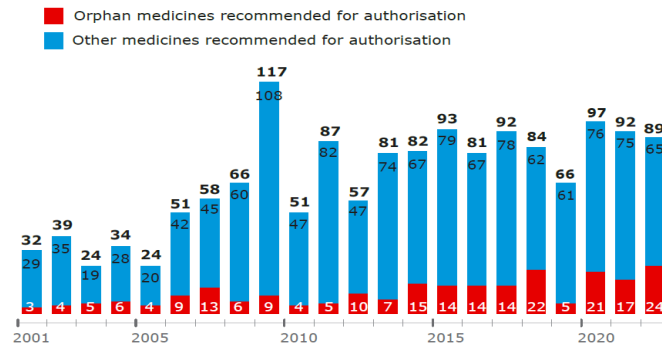
over **230** orphan medicines authorised in the EU



Number of medicines that have received an orphan designation (2001-2022)

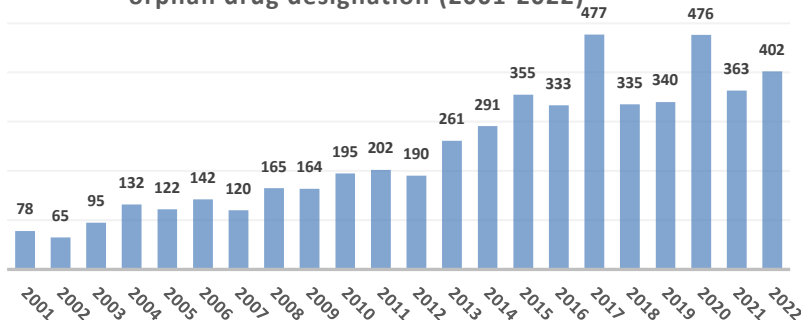


Number of orphan medicines recommended for authorisation (2001-2022)



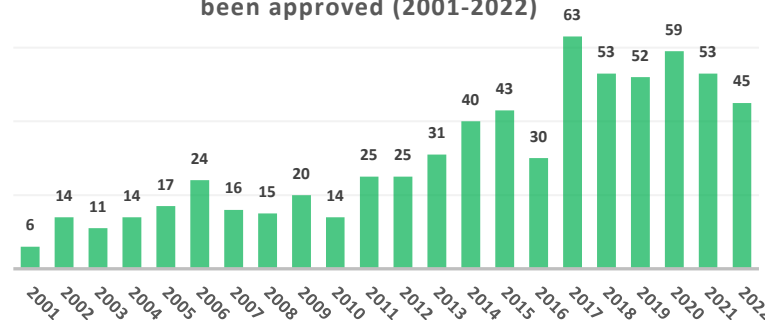
over **5300** products with Orphan Drug Designation

Number of products that have received a US FDA orphan drug designation (2001-2022)



670 Approved Orphan Drug-designated Products

Number of orphan-designated products that have been approved (2001-2022)



One Dataset, Two Manuscripts

FDA

Fermaglich and Miller
Orphanet Journal of Rare Diseases (2023) 18:163
<https://doi.org/10.1186/s13023-023-02790-7>

Orphanet Journal of
Rare Diseases

RESEARCH Open Access

A comprehensive study of the rare diseases and conditions targeted by orphan drug designations and approvals over the forty years of the Orphan Drug Act

Lewis J. Fermaglich^{1*} and Kathleen L. Miller¹

Abstract
Background Rare diseases affect more than 30 million Americans. The passage of the Orphan Drug Act (ODA) in the United States in 1983 represented a launching point for a rare disease drug development revolution for these patients. Financial incentives provided by the ODA through its Orphan Drug Designation Program, in addition to remarkable scientific advances over the past 40 years, have led to hundreds of drug approvals for rare diseases. Our research examines the rare diseases that have been targeted by orphan drug designations and subsequent approvals since the law was enacted.
Methods Using an internal FDA database, we classified and analyzed all orphan drug designations and approvals from 1983 to 2022 by disease and therapeutic area.
Results Over the 40 years of the ODA, 6,340 orphan drug designations were granted, representing drug development for 1,079 rare diseases. Additionally, 882 of those designations resulted in at least one FDA approval for use in 392 rare diseases. Much of this development has been concentrated in oncology as seven of the top ten most designated and approved diseases were rare cancers.
Conclusions Researchers have estimated that there may be 7000–10,000 rare diseases that have been identified and described. Based on our study, we can conclude that around 5% of rare diseases have an FDA-approved drug and up to 15% of rare diseases have at least one drug that has been developed and shown promise in their treatment, diagnosis or prevention. Funding of basic and translational science for rare disease drug development should continue in order to bring therapies to the millions of affected patients who remain without treatment options.

Focused on trends in
targeted **DISEASES**

Focused on trends in
designated **DRUGS**

EXPERT OPINION ON ORPHAN DRUGS
<https://doi.org/10.1080/21678707.2021.2047021>

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ORIGINAL RESEARCH

Drugs and biologics receiving FDA orphan drug designation: an analysis of the most frequently designated products and their repositioning strategies

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Office of Orphan Products Development, Office of Clinical Policy and Programs, Office of the Commissioner, US Food and Drug Administration

ABSTRACT

Background: The Orphan Drug Act was created to stimulate the development of drugs and biologics for rare diseases. Investigating products that have received orphan drug designation provide a greater understanding of rare disease drug development, as well as the repositioning business models of developers.

Research design and methods: We used a dataset containing all orphan drug designations between 1983 and 2019. To analyze the orphan products, we constructed a variable, 'unique product,' that allowed for the standardization of generic names of drugs and biologics. Additional analysis was performed on the most frequently designated unique products and their repositioning strategies.

Results: We found 5,099 orphan drug designations representing 3,269 unique products, of which 508 had an orphan-designated approval from FDA. Unique products with only a single designation represented 2,448 (75%) of the total products and 26 (1%) products had 10 or more designations. Over 60% of these unique products with 10 or more designations were antineoplastics or immunomodulators.

Conclusions: The most designated unique products revealed a continuum of repositioning strategies, from the repurposing of approved drugs to parallel indication development programs for recently developed drugs. The fact that over 3,000 unique products have been studied for rare diseases indicates that future repositioning opportunities may become increasingly available.

ARTICLE HISTORY

Received 24 October 2021
Accepted 23 February 2022

KEYWORDS

Orphan designation; orphan drug act; rare disease; repositioning; repurposing; US food and drug administration

Disease Aggregation



- Single medical concept from designation phrase (using “*Mondo*” dataset)
- Based on target patient population that would benefit from drug
- Designations for:
 - conditions that were complications of underlying diseases
 - side effects of treatments for the underlying diseases, or
 - opportunistic diseases (e.g., cryptococcal meningitis or bronchiectasis) primarily associated with underlying diseases (e.g., HIV/AIDS or cystic fibrosis, respectively)were classified as the underlying disease

Product Standardization



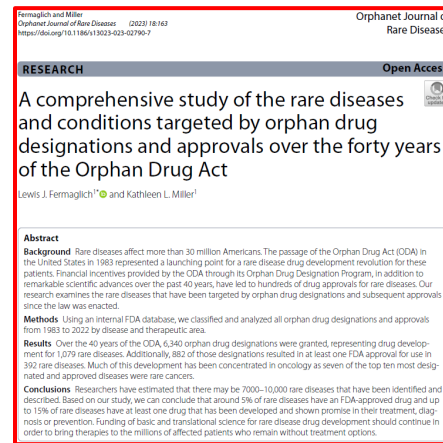
- “Unique product”: allowed for the standardization of generic product names
- Pharmaceutical salts, isomers, enantiomers, recombinant versions of products, and formulations (tablet, capsules, oral solution) were not considered “unique”
- Differs from the regulatory definitions of “same drug”

Orphan Drug Designations and Approvals, 1983-2022:

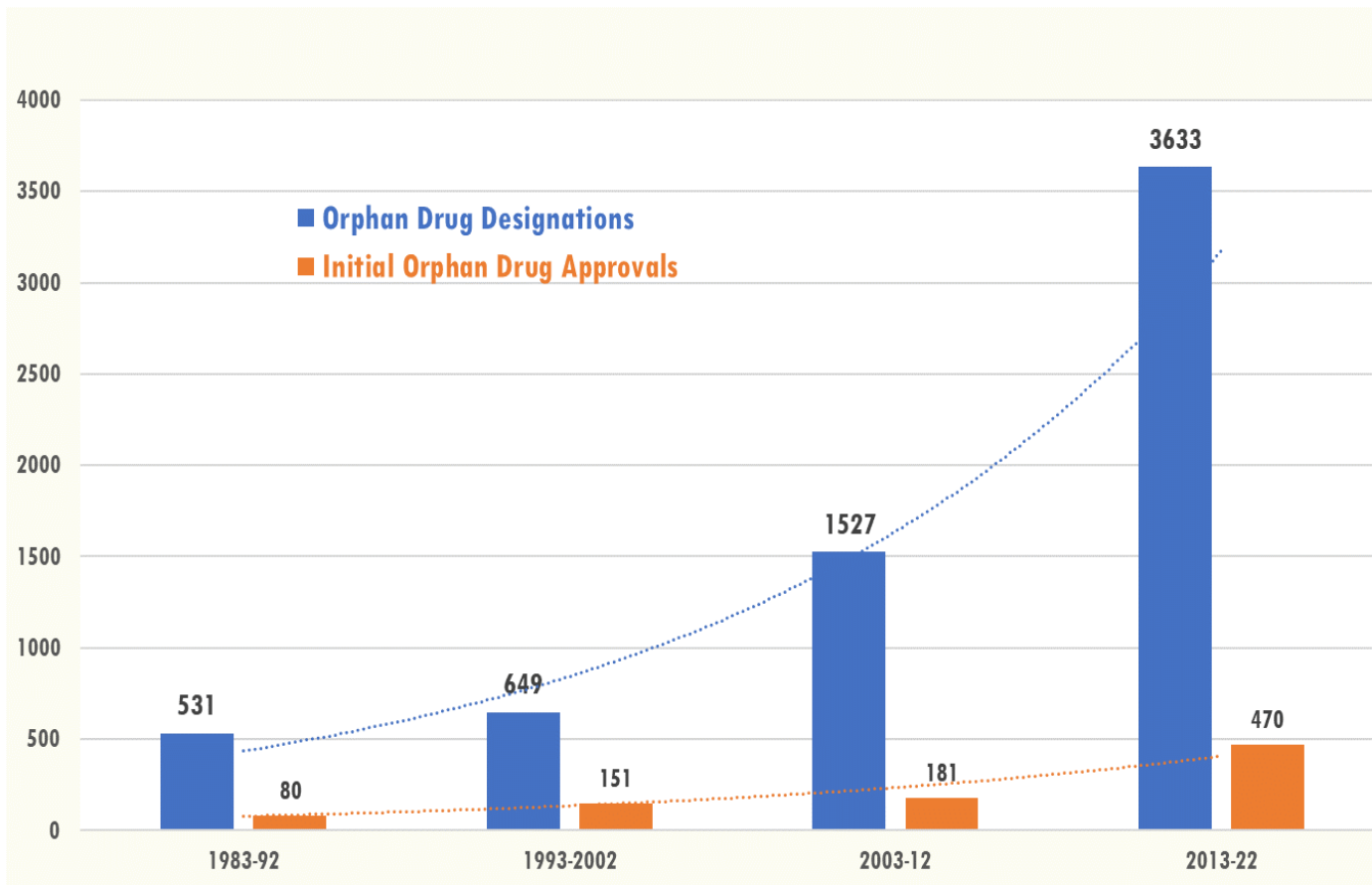
DISEASE Overview



- **6,340** designations
- **882** (14%) first approvals
- Distilled down to:
 - **1,079** individual diseases with at least one orphan designated product
 - **392** rare diseases with at least one marketing approval



Orphan Drug Designations and Initial Approvals by Decade, 1983—2022



Orphan drug designations and initial orphan drug approvals, by therapeutic area, 1983-2022



| Therapeutic Area | Designations % (6340) | Initial Orphan Drug Approvals % (882) |
|---|-----------------------|---------------------------------------|
| Oncology | 38% (2405) | 38% (333) |
| Neurology | 14% (892) | 10% (84) |
| Infectious Diseases | 7% (461) | 10% (90) |
| Metabolism | 6% (370) | 7% (61) |
| Hematology | 5% (306) | 8% (69) |
| Pulmonary | 4% (280) | 2% (19) |
| Gastroenterology | 4% (243) | 3% (25) |
| Transplant | 4% (239) | 2% (18) |
| Ophthalmology | 3% (200) | 2% (19) |
| Vascular | 2% (155) | 2% (21) |
| Rheumatology | 2% (150) | 3% (26) |
| Endocrinology | 2% (147) | 5% (43) |
| Dermatology | 2% (103) | 1% (8) |
| Pharmacology/Toxicology/Poisoning/Chelators | 2% (99) | 2% (22) |
| Nephrology/Urology | 1% (86) | 2% (15) |
| Immunology | 1% (76) | 2% (14) |
| Cardiology | 1% (50) | 1% (8) |
| Orthopedics | 1% (43) | <1% (4) |
| Obstetrics and Gynecology | <1% (19) | <1% (2) |
| ENT | <1% (10) | <1% (0) |
| Nutrition | <1% (6) | <1% (1) |

Rare diseases with the most orphan drug designations, 1983-2022



| DISEASE | Therapeutic Area | Designations | Initial Orphan Drug Approvals |
|-------------------------------------|---------------------|--------------|-------------------------------|
| malignant pancreatic neoplasm | Oncology | 185 | 4 |
| acute myeloid leukemia | Oncology | 183 | 14 |
| multiple myeloma | Oncology | 130 | 19 |
| glioma | Oncology | 129 | 4 |
| metastatic melanoma | Oncology | 120 | 16 |
| amyotrophic lateral sclerosis | Neurology | 119 | 5 |
| cystic fibrosis | Pulmonary | 108 | 8 |
| HIV infectious disease* | Infectious Diseases | 92 | 23 |
| ovarian cancer* | Oncology | 91 | 8 |
| hepatocellular carcinoma | Oncology | 89 | 11 |
| gastric cancer | Oncology | 80 | 4 |
| glioblastoma | Oncology | 78 | 0 |
| idiopathic pulmonary fibrosis | Pulmonary | 76 | 2 |
| sickle cell disease | Hematology | 68 | 5 |
| graft versus host disease | Transplant | 63 | 3 |
| Duchenne muscular dystrophy | Neurology | 63 | 5 |
| pulmonary arterial hypertension | Vascular | 58 | 9 |
| B-cell chronic lymphocytic leukemia | Oncology | 57 | 12 |
| soft tissue sarcoma | Oncology | 56 | 6 |
| acute lymphoblastic leukemia | Oncology | 55 | 8 |
| solid organ transplant rejection | Transplant | 49 | 7 |
| myelodysplastic syndrome | Oncology | 49 | 5 |
| Huntington disease | Neurology | 46 | 2 |
| small cell lung carcinoma | Oncology | 43 | 5 |
| systemic sclerosis | Rheumatology | 42 | 1 |

Of top 25 most-designated rare diseases, ~60% are indicated for rare cancers

Orphan drug designated rare diseases with the most approvals , 1983-2022



| DISEASE | Therapeutic Area | Initial Orphan Drug Approvals | Designations |
|---|---------------------|-------------------------------|--------------|
| HIV infectious disease* | Infectious Diseases | 23 | 92 |
| multiple myeloma | Oncology | 19 | 130 |
| non-small cell lung carcinoma | Oncology | 18 | 35 |
| metastatic melanoma | Oncology | 16 | 120 |
| acute myeloid leukemia | Oncology | 14 | 183 |
| B-cell chronic lymphocytic leukemia | Oncology | 12 | 57 |
| hepatocellular carcinoma | Oncology | 11 | 89 |
| follicular lymphoma | Oncology | 11 | 37 |
| isolated congenital growth hormone deficiency | Endocrinology | 10 | 23 |
| pulmonary arterial hypertension | Vascular | 9 | 58 |
| hemophilia B | Hematology | 9 | 23 |
| ovarian cancer* | Oncology | 8 | 91 |
| diffuse large B-cell lymphoma | Oncology | 8 | 33 |
| cystic fibrosis | Pulmonology | 8 | 108 |
| chronic myelogenous leukemia | Oncology | 8 | 38 |
| acute lymphoblastic leukemia | Oncology | 8 | 55 |
| solid organ transplant rejection | Transplant | 7 | 49 |
| thyroid cancer | Oncology | 7 | 13 |
| Lennox-Gastaut syndrome | Neurology | 7 | 16 |
| soft tissue sarcoma | Oncology | 6 | 56 |
| neuroendocrine neoplasm | Oncology | 6 | 24 |
| malaria | Infectious Diseases | 6 | 28 |
| mantle cell lymphoma | Oncology | 6 | 23 |
| homozygous familial hypercholesterolemia | Metabolism | 6 | 16 |
| immune thrombocytopenic purpura | Hematology | 6 | 22 |

Of top 25 most-approved rare diseases, **60%** are for rare cancers

of Designations by DISEASE



- Multiple designations for particular diseases:
 - **7** diseases had more than 100 designated products each (accounting for 974/6340 or 15% of all designations)
 - **58** diseases had 20 or more designated products each (accounting for 3004/6340 or 47% of all designations)
 - **442** diseases have only **one** designation

DISEASE Conclusions



- Using a range of estimates for the total number of rare diseases (7,000-10,000), we can calculate:
 - **4-6%** of rare diseases have at least one marketing approval
 - **11-15%** of rare diseases have had at least one product that has shown some promise for use in diagnosing, preventing, or treating them

Orphan Drug Designations, 1983-2019:

PRODUCT Overview



- **3,269** unique **products**:
 - **508** (16%) had at least one associated approval
 - **2,448** (75%) with only a single designation
 - **26 (1%)** unique products had **≥ 10 designations**
 - **Designations: 60%** drugs, **40%** biologics – stable over time
 - **Approvals: 63%** drugs, **37%** biologics



Unique products with 10 or more orphan drug designations

| Unique Product | # of Designations | # of Orphan Designated Approvals | Product Type | Primary Product Effect | Designated Targeted Therapeutic Area(s) |
|-------------------------------------|-------------------|----------------------------------|----------------|----------------------------|---|
| Interferon Alfa | 30 | 4 | Biologic | Immunostimulant | Onc (22); ID (5); Rheum (2); Heme (1) |
| Alpha-1 Proteinase Inhibitor | 21 | 1 | Biologic | Antihemorrhagic | Pulm (13); TP (5); Endo (2); ID (1) |
| Immune Globulin | 21 | 5 | Biologic | Immune System Product | Neuro (10); Rheum (5); ID (2); Card, GI, Heme, Imm (1) |
| Somatropin | 21 | 16 | Biologic | Hormone | Endo (14); ID (4); Derm, GI, Ob/Gyn (1) |
| Cannabidiol | 19 | 2 | Small Molecule | Nervous System Product | Neuro (12); TP (3); Onc (2); Derm, GI (1) |
| Paclitaxel | 19 | 2 | Small Molecule | Antineoplastic | Onc (19) |
| Cyclosporine | 17 | 0 | Small Molecule | Immunosuppressant | TP (8); Ophtho (4); Neuro, Pulm (2); ID (1) |
| Sirolimus | 16 | 1 | Small Molecule | Immunosuppressant | Derm (6); Pulm (3); Heme, Vasc (2); GI, Onc, Ophtho (1) |
| Thalidomide | 15 | 2 | Small Molecule | Immunosuppressant | ID, Onc (4); GI, TP (3); Vasc (1) |
| Ibrutinib | 14 | 8 | Small Molecule | Antineoplastic | Onc (13); TP (1) |
| Nitric Oxide | 14 | 2 | Small Molecule | Respiratory System Product | Pulm (6); Vasc (4); ID (2); Heme, Imm (1) |
| Amphotericin B | 13 | 3 | Small Molecule | Anti-infective | ID (13) |
| Doxorubicin | 13 | 2 | Small Molecule | Antineoplastic | Onc (13) |
| Interferon Beta | 13 | 2 | Biologic | Immunostimulant | Onc (5); ID, Neuro (3); Pulm, Rheum (1) |
| Melatonin | 13 | 0 | Small Molecule | Nervous System Product | Neuro (5); GI, Onc, Pharm (2); Metab, Vasc (1) |
| Coagulation Factor VIIa | 12 | 7 | Biologic | Antihemorrhagic | Heme (10); Pulm, Vasc (1) |
| Pembrolizumab | 12 | 8 | Biologic | Antineoplastic | Onc (12) |
| Phenylbutyrate | 12 | 2 | Small Molecule | Metabolism Product | Metab (5); Neuro (4); Onc (2); Heme (1) |
| Angiotensin (1-7) | 11 | 0 | Small Molecule | Vasodilator ³ | Neuro, TP (3); Onc (2); Derm, Pharm, Vasc (1) |
| Bevacizumab | 11 | 5 | Biologic | Antineoplastic | Onc (9); Ophtho, Vasc (1) |
| Brentuximab | 11 | 4 | Biologic | Antineoplastic | Onc (11) |
| Sargramostim | 11 | 3 | Biologic | Immunostimulant | Onc (5); Pulm, TP (2); Derm, Pharm (1) |
| Arsenic | 10 | 1 | Small Molecule | Antineoplastic | Onc (9); TP (1) |
| Filgrastim | 10 | 6 | Biologic | Immunostimulant | Onc (3); Pharm, TP (2); Imm, ID, Neuro (1) |
| Melphalan | 10 | 2 | Small Molecule | Antineoplastic | Onc (9); TP (1) |
| Nivolumab | 10 | 4 | Biologic | Antineoplastic | Onc (10) |



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