The impact of the Orphan Drug Act on Food and Drug Administration-approved therapies for rare skin diseases and skin-related cancers

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The Orphan Drug Act of 1983 (ODA) put in place a set of financial and marketing incentives to stimulate the development of drugs to treat rare diseases, and since its passage, more than 600 orphan drug and biologic products have been brought to market in the United States. Rapid growth in orphan drug approvals in conjunction with high orphan drug prices have triggered concern that drug makers are exploiting certain aspects of the ODA for financial gain and that some pharmaceutical drugs are receiving orphan status where it is not warranted. The landscape of approved therapies for rare skin diseases has not been well described. In this article, we provide a descriptive analysis of the United States Food and Drug Administration-approved orphan drugs for the treatment of rare dermatologic conditions and skin-related cancers since the enactment of the ODA. We discuss policy issues that emerge from the analysis and suggest areas for future research. Next, we elucidate ODA loopholes using dermatologic drugs as examples and propose potential reforms. Finally, we consider future directions for orphan drug development in the field of dermatology. (J Am Acad Dermatol 2019;81:867-77.)

Key words: drug approvals; Food and Drug Administration; orphan drugs; Orphan Drug Act; rare skin diseases; pharmaceutical drugs.

BACKGROUND

Drugs to treat rare diseases were once unattractive investment opportunities owing to limited sales volume and expected profit relative to the steep costs involved in drug development, manufacture, and sale. Enactment of the Orphan Drug Act of 1983 (ODA) in the United States (US) tipped the scales by establishing a set of financial and marketing incentives to promote the development of drugs to treat rare diseases, statutorily defined as those diseases or conditions that affect fewer than 200,000 individuals in the US or those diseases that affect more than 200,000 individuals but for which the cost of making and marketing a drug cannot be reasonably recaptured from sale of the drug.[1]

ODA provisions include a 7-year period of exclusive rights to market an orphan drug after US Food and Drug Administration (FDA) approval, a 25% tax credit for clinical trial costs (recently lowered from a 50% tax credit[2]), and exemption from user fees required for FDA review under the Prescription Drug User Fee Act (approximately $2.5 million per new drug application in 2019[3]). With these incentives in place, more than 600 drugs and biologic agents to treat rare diseases have been brought to market since passage of the ODA more than 35 years ago.[4]

A concomitant blossoming of genomic research has brought to light previously unknown disease mechanisms and potential therapeutic targets. The

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1990s and 2000s saw progress in the identification of genes underlying several rare skin disorders, including epidermolysis bullosa simplex, the ectodermal dysplasias, and ichthyoses.[5] Rapid, low-cost genome sequencing and the advent of gene therapy have enabled the identification and subsequent replacement, correction, or inactivation of mutated genes.[6,7] The era of precision medicine promises to usher in therapies that target personalized genome-level variants.

An upsurge in the number of orphan drugs approved in recent years and extremely high prices for these drugs have triggered concern among patients, payors, and policymakers that drug makers may be "gaming the system" of ODA incentives.[8-12] The average annual per-patient cost of an orphan drug in 2018 was more than 4 times the cost of a nonorphan drug (approximately $150,900 vs $33,700, respectively).[13] Although orphan drug expenditures comprise roughly one-tenth of total pharmaceutical expenditures,[14] the high price of some orphan drugs imposes a burden on patients in the form of out-of-pocket costs while yielding profits for drug companies even in the face of relatively small numbers of patient users.[13,15,16]

Three principal ODA "loopholes" have been recognized. First, drug companies can seek orphan designation and approval for narrow subsets of more common diseases, termed "salami-slicing."[11,17,18]

Second, a drug that has been on the market for a nonorphan condition may later receive approval for an orphan indication, a practice that falls under the umbrella of "drug repurposing."[8,19] Repurposed orphans receive the same statutory incentives as orphan drugs that first came to market for treatment of a rare disease.

Third, a single drug receives a new 7-year exclusivity period for each approved orphan indication, which could prolong market exclusivity beyond a drug's patent term.[20] Exclusivity that outlasts the patent term for even a small number of drugs can cost taxpayers significant sums by delaying generic entry beyond what legislators intended as a quid pro quo "reward" for pharmaceutical innovation.

The landscape of approved therapies for rare skin diseases has not been described in the academic literature. This article provides a descriptive and policy analysis of orphan drug approvals for rare dermatologic conditions and skin-related cancers since the passage of the ODA. We illustrate the most notable ODA loopholes using dermatologic drugs as examples and propose several reforms to better align the current system with the original intent of the ODA. Finally, we forecast the direction of future orphan drug development in dermatology.

CAPSULE SUMMARY

- As a result of the incentives for rare disease drug development contained within the Orphan Drug Act, 72 indications have been approved for rare skin diseases, skin-related cancers, and hereditary disorders with prominent dermatologic manifestations.
- We provide an analysis of dermatologic orphan drug approvals and forecast future drug development trends.

METHODS

Table I provides definitions of common terms relating to the US drug-approval process. Of note, providers may prescribe drugs "off-label" for unapproved uses where those uses are medically warranted.[21] We do not consider off-label uses in this article.

The primary data source for this analysis was the publicly available FDA Orphan Drug Product database.[22] A master list of all orphan drugs approved from January 1, 1983, to December 31, 2018, was searched to identify drugs approved for primary dermatologic conditions and cancers of cutaneous origin. Multisystem hereditary conditions with prominent dermatologic manifestations were included and confirmed for relevance by an expert reviewer (M.A.). Orphan drugs designated but not approved were excluded from the analysis.

For each drug, the generic and trade names, designation date, designation, approved indication, marketing approval date, exclusivity end date, and drug company sponsor were extracted. Each drug was classified into 1 of 6 disease categories: infectious, immunologic, inflammatory, hereditary, oncologic, and other. Each drug was also classified by type (small molecule, monoclonal antibody, or other protein-based therapy) using the DrugBank database.[23] The percentage of indications for cancer- and non–cancer-related skin conditions that had a pharmaceutical company sponsor among the top 10 drug companies by global revenue (Pfizer, Novartis, Roche, Johnson & Johnson, Sanofi, Merck, GlaxoSmithKline, AbbVie, Bayer, and AstraZeneca) was determined.[24] Several dermatologic drugs that exemplify ODA loopholes were identified and used to explain how these loopholes potentially undermine the intent of the ODA.

RESULTS

We found 72 FDA-approved indications that met inclusion criteria for treatment of dermatologic

Abbreviations used:

FDA: Food and Drug Administration
HS: hidradenitis suppurativa
ODA: Orphan Drug Act of 1983
US: United States

conditions, and which constituted approximately 10% of all approved orphan indications since passage of the ODA in 1983 (Fig 1). To put this in perspective, at least 7000 rare diseases have been identified, of which upwards of 1000 are estimated to be dermatologic diseases.[25-27]

During the first 14 years after passage of the ODA (1983 to 1997), 10 indications were approved for skin conditions and skin-related cancers, 24 indications were approved during the next 14-year period (1998 to 2011), and 38 indications were approved during the last 7 years (2012 to 2018). The mean time from orphan designation to marketing approval was 4.7 years (median, 3.25 years; range, 3 months-24.7 years). Of the 72 orphan conditions, 37 (51.4%) were approved for skin-related cancers, 21 (29.2%) for hereditary disorders, 7 (9.7%) for infectious diseases, 3 (4.2%) for inflammatory disorders, 2 (2.8%) for immunologic diseases, and 2 (2.8%) for other diseases and conditions (Table II). Fig 2 provides a graphical illustration of these approvals over time according to disease category. Twelve of the 72 dermatologic orphan indications (16.7%) were specified for use in pediatric or adolescent patients. Fourteen of the 72 indications (19.4%) targeted a biomarker-derived subset; of these, 10 indications were specified for treatment of melanoma containing *BRAF* V600E, V600K, or V600 wild-type mutations.

Eleven therapies were approved for more than 1 dermatologic orphan indication: 9 drugs or drug combinations were approved for 2 dermatologic indications each, and 2 drugs—ipilimumab and pembrolizumab—were each approved for 3 dermatologic indications. Tallying every drug once, there were 59 distinct drug products approved for dermatologic conditions. Of these, 29 (49.2%) were small molecule drugs, 10 (16.9%) were monoclonal antibodies, and 20 (34%) were protein-based therapies, including interferons, blood factors, and immunoglobulins. Of the 59 drugs, 39 (66.1%) were approved for a single rare disease or condition, and 20 drugs (33.9%) had approvals for multiple rare diseases.

The pharmaceutical company sponsors with the largest number of dermatologic orphan indications were Novartis (9), Bristol-Myers Squibb (7), Shire and its subsidiary Dyax (5), Merck (4), Celgene (3), BioMarin (3), and Eisai (3). Among indications for skin-related cancers (n = 37), 19 (51.4%) had a pharmaceutical company sponsor in the top 10 drug companies by global revenue. In contrast, among indications for non—cancer-related skin conditions (n = 35), only 6 (17.1%) had a sponsor among the top 10 drug companies.

DISCUSSION

The upward trend in orphan drug approvals for skin diseases and skin-related cancers mirrors the overall trend in orphan drug approvals (Fig 1).[28] The climbing rate of approvals reflects several forces at work: an increased awareness of and attention to rare diseases, a market that tolerates extremely high prices for orphan drugs, and the new-found ability to extend exclusivity for potentially lucrative orphan drugs. In recent years, infectious diseases have been infrequent targets of new therapies, with only 2 infectious disease therapeutics (for varicella zoster and leishmaniasis) approved in the past decade. Similarly, few drugs have been approved to treat autoimmune and inflammatory disorders. The only orphan drug approved for a blistering disorder was rituximab for treatment of pemphigus vulgaris in 2018. However, several therapies are in the pipeline, including a gene therapy for recessive dystrophic epidermolysis bullosa involving intradermal injections of genetically modified fibroblasts,[29] an investigational monoclonal antibody in early-phase clinical development for pemphigus vulgaris and pemphigus foliaceus,[30] and a C5 and leukotriene B4 inhibitor under development for bullous pemphigoid.[31]

Over the past decade, a number of drugs were approved to treat hereditary disorders with prominent skin involvement caused by enzyme deficiencies, including the mucopolysaccharidoses and Fabry disease. Many genodermatoses remain without effective treatment options, such as the nonacute porphyrias, syndromic and nonsyndromic ichthyoses, the ectodermal dysplasias, and precancerous conditions such as xeroderma pigmentosum.

Orphan drug approvals for cancers of cutaneous origin dominated among dermatologic orphan drug approvals, with melanoma constituting the leading disease target. Anticancer drug predominance in our cohort is consistent with findings of a predominance of anticancer therapies in orphan drug development overall.[32] Targeting research and development investment in oncology drugs may be a strategic business decision: owing to the versatility of their use for multiple cancer types, orphan oncology drugs can offer a higher profit potential than can noncancer orphan therapies.[33]

Table I. Definitions of common terms relating to the US drug-approval process

Term	Definition
Drug or therapy	In this article, we use the terms "drug" and "therapy" interchangeably to describe a pharmaceutical drug or biologic product within the purview of the US FDA.
Orphan designation (orphan status)	A status granted by the FDA's Office of Orphan Products Development to a drug meeting statutory criteria for orphan status that enables the drug's sponsor (ie, the drug maker) to receive the incentives promulgated within the ODA. The drug's sponsor typically seeks orphan status for a drug by request to the FDA before submitting a new drug application, biologics license application, or supplemental application for US marketing approval.
Orphan drug approval	A drug with orphan status that has been granted marketing approval after an adequate demonstration of safety and efficacy.
Indication(s)	FDA-approved use(s) of a drug that appear on the drug's label.
Distinct drug product(s)	A single drug may receive marketing approval for more than 1 orphan indication. For this reason, we occasionally refer to tallies of "distinct drug products," a term we use to clarify that every drug is counted only once even if it has been approved for more than 1 indication.

FDA, Food and Drug Administration; *ODA*, Orphan Drug Act; *US*, United States.

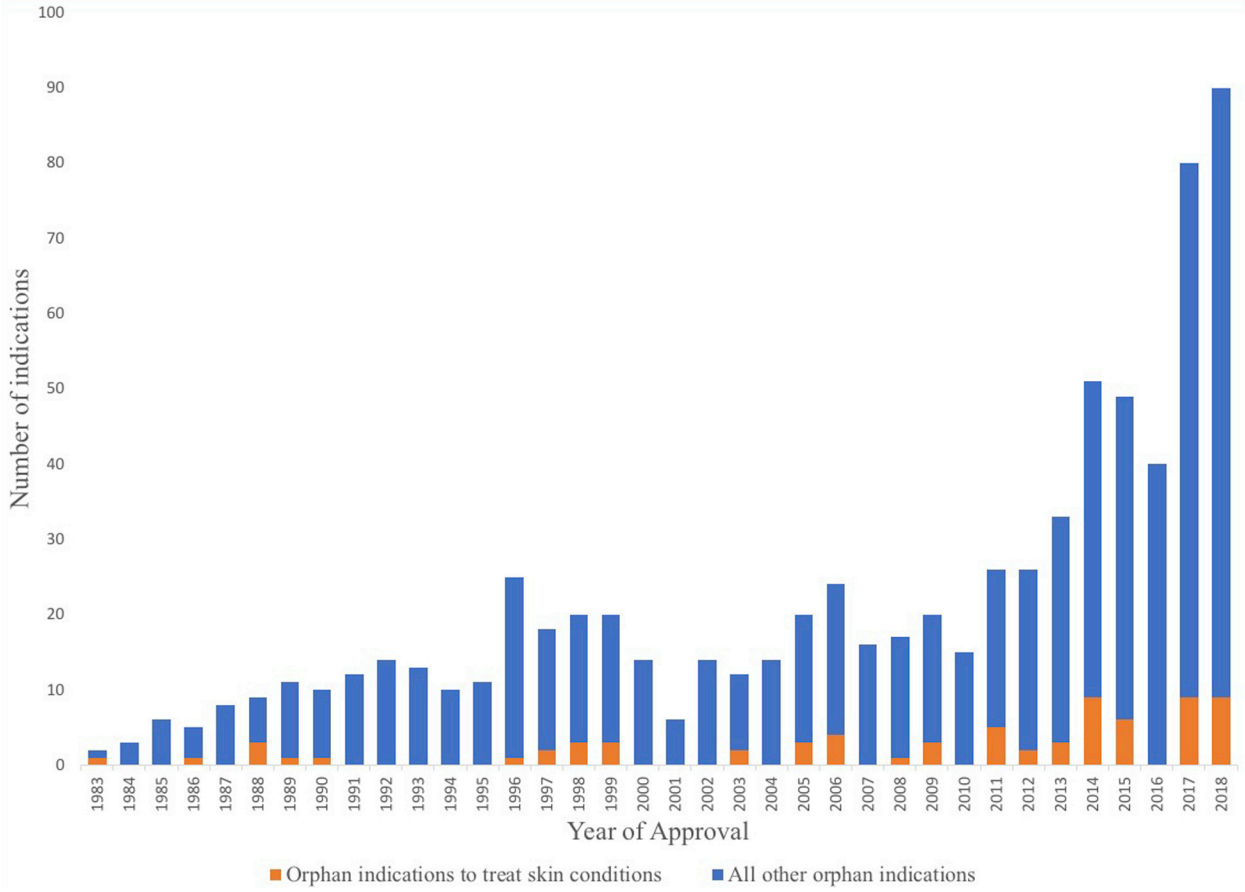

Fig 1. Orphan indications approved by the United States Food and Drug Administration for dermatologic conditions from 1983 to 2018 compared with all approved orphan indications. Note: Approximately 10% of all approved orphan indications treat dermatologic conditions.

An estimated 50% of rare diseases occur in children.[34] This contrasts with our finding that only 17% of approved indications for rare dermatologic conditions were specified for use in pediatric or adolescent patients. The discrepancy can be at least partly attributed to the challenges of conducting pediatric clinical trials.[35,36] Research suggests that legislation such as the US FDA Modernization Act of

Table II. Orphan drugs approved to treat dermatologic conditions, by disease category*

Drug	Treatment
Infectious	
1. Clofazimine	Treatment of lepromatous leprosy, including dapsone-resistant lepromatous leprosy and lepromatous leprosy complicated by erythema nodosum leprosum.
2. Thalidomide	Acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum and as maintenance therapy for prevention and suppression of the cutaneous manifestations of erythema nodosum leprosum recurrences.
3. Miltefosine	Treatment of visceral leishmaniasis due to *Leishmania donovani*; cutaneous leishmaniasis due to *Leishmania braziliensis*, *Leishmania guyanensis*, and *Leishmania panamensis*; and mucosal leishmaniasis due to *Leishmania braziliensis*.
4. Liposomal amphotericin B	Treatment of visceral leishmaniasis.
5. Varicella zoster immune globulin	Postexposure prophylaxis of varicella in high-risk individuals to reduce the severity of varicella.
6. Vaccinia immune globulin	Indication 1: Treatment and modification of aberrant infections induced by vaccinia virus that include its accidental implantation in eyes (except in cases of isolated keratitis), mouth, or other areas where vaccinia infection would constitute a special hazard; eczema vaccinatum; progressive vaccinia; severe generalized vaccinia, and vaccinia infections in individuals who have skin conditions such as burns, impetigo, varicella zoster, or poison ivy; or in individuals who have eczematous skin lesions because of the activity or extensiveness of such lesions.
7. Vaccinia immune globulin	Indication 2: Treatment and/or modification of the following conditions, which are complications resulting from smallpox vaccination: eczema vaccinatum; progressive vaccinia; severe generalized vaccinia; vaccinia infections in individuals who have skin conditions such as burns, impetigo, varicella zoster, or poison ivy, or in individuals who have eczematous skin lesions because of the activity or extensiveness of such lesions; aberrant infections induced by vaccinia virus that include its accidental implantation in eyes (except in cases of isolated keratitis), mouth, or other areas where vaccinia infection would constitute a special hazard.
Immunologic	
1. Rituximab	Treatment of adult patients with moderate to severe pemphigus vulgaris.
2. Ibrutinib	Treatment of adult patients with chronic graft versus host disease.
Inflammatory	
1. Topical metronidazole	Treatment of acne rosacea.
2. Adalimumab	Indication 1: Treatment of moderate to severe hidradenitis suppurativa (Hurley stage 2 and Hurley stage 3 disease).
3. Adalimumab	Indication 2: Treatment of moderate to severe hidradenitis suppurativa in patients 12 years old and older.
Hereditary	
1. Hemin	Amelioration of recurrent attacks of acute intermittent porphyria (AIP) temporarily related to the menstrual cycle in susceptible women and similar symptoms which occur in other patients with AIP, porphyria variegata, and hereditary coproporphyria.
2. Midostaurin	Treatment of adult patients with aggressive systemic mastocytosis, systemic mastocytosis with associated hematological neoplasm, or mast cell leukemia.
3. Cromolyn sodium	Treatment of mastocytosis.
4. Imatinib mesylate	Indication 1: Treatment of adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation or with c-Kit mutational status unknown. Indication 2: Oncologic.
5. Interferon gamma 1-b	Treatment of chronic granulomatous disease.
6. Ceramide trihexosidase/ alpha-galactosidase A	For use in patients with Fabry disease to reduce globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types.

Continued

Table II. Cont'd

Drug	Treatment
7. Migalastat hydrochloride	Treatment of adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase alpha (*GLA*) gene variant based on in vitro assay data.
8. Laronidase	Treatment for patients with Hurler and Hurler-Scheie forms of MPS I and for patients with the Scheie form who have moderate to severe symptoms.
9. N-acetylgalactosamine-4-sulfatase-recombinant human	For patients with MPS VI (Maroteaux-Lamy syndrome). Galsulfase has been shown to improve walking and stair-climbing capacity.
10. Idursulfase	Indicated for patients with Hunter syndrome (MPS II). Idursulfase has been shown to improve walking capacity in these patients.
11. Vestronidase alfa-vjbk	Treatment of MPS type VII (Sly syndrome) in pediatric and adult patients.
12. Elosulfase alfa	Patients with MPS type IVA (Morquio A syndrome).
13. C1-esterase inhibitor (human, pasteurized)	For routine prophylaxis to prevent hereditary angioedema attacks in adolescent and adult patients.
14. C1-esterase inhibitor (recombinant)	Treatment of acute attacks of hereditary angioedema in adult and adolescent patients.
15. C1-esterase inhibitor (human)	Indication 1: Routine prophylaxis against angioedema attacks in patients with hereditary angioedema.
16. C1-esterase inhibitor (human)	Indication 2: Routine prophylaxis against angioedema attacks in adults, adolescents, and pediatric patients (6 years old and older) with hereditary angioedema.
17. Ecallantide	Indication 1: Treatment of acute attacks of hereditary angioedema in patients 16 years old and older.
18. Ecallantide	Indication 2: Treatment of acute attacks of hereditary angioedema in patients 12 years old and older.
19. Icatibant	Treatment of acute attacks of hereditary angioedema in adults 18 years old and older.
20. Lanadelumab-flyo	Prophylaxis to prevent attacks of hereditary angioedema in patients 12 years old and older.
21. Everolimus	Treatment of adults with renal angiomyolipoma and tuberous sclerosis complex (TSC), including TSC-associated subependymal giant cell astrocytoma, TSC-associated angiomyolipoma, and TSC-associated lymphangioleiomyomatosis, not requiring immediate surgery.
Oncologic	
1. Interferon alfa-2a (recombinant)	Treatment of AIDS-related Kaposi sarcoma.
2. Interferon alfa-2b (recombinant)	Treatment of selected patients with AIDS-related Kaposi sarcoma.
3. Daunorubicin citrate liposome injection	First-line cytotoxic therapy for advanced, HIV-related Kaposi sarcoma.
4. Paclitaxel	For the second-line treatment of AIDS-related Kaposi sarcoma.
5. Alitretinoin	Topical treatment of cutaneous lesions in patients with AIDS-related Kaposi sarcoma.
6. Ipilimumab	Indication 1: For the adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm, who have undergone complete resection including total lymphadenectomy.
7. Ipilimumab	Indication 2: Treatment of unresectable or metastatic melanoma.
8. Ipilimumab	Indication 3: An expansion of the indication for the treatment of unresectable or metastatic melanoma in pediatric patients (12 years old and older).
9. Denileukin diftitox	Treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the interleukin 2 receptor.
10. Bexarotene	Treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.
11. Brentuximab vedotin	Indication 1: For adult patients with primary cutaneous anaplastic large cell lymphoma who have received prior systemic therapy.
12. Brentuximab vedotin	Indication 2: Treatment for adult patients with CD30-expressing mycosis fungoides who have received prior systemic therapy.

Continued

Table II. Cont'd

Drug	Treatment
13. Mogamulizumab	Treatment of adult patients with relapsed or refractory mycosis fungoides or Sézary syndrome after at least 1 prior systemic therapy.
14. Mechlorethamine	Topical treatment of stage 1A and 1B mycosis fungoides-type cutaneous T-cell lymphoma in patients who have received prior skin-directed therapy.
15. Belinostat	Treatment of patients with relapsed or refractory peripheral T-cell lymphoma.
16. Pralatrexate	Treatment of patients with relapsed or refractory peripheral T-cell lymphoma.
17. Romidepsin	Indication 1: Treatment of cutaneous T-cell lymphoma in patients who have received at least one prior systemic therapy.
18. Romidepsin	Indication 2: Treatment of peripheral T-cell lymphoma in patients who have received at least 1 prior therapy.
19. Imatinib mesylate	Indication 2: Treatment of adult patients with unresectable, recurrent, and/or metastatic dermatofibrosarcoma protuberans.
20. Vorinostat	Treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma who have progressive, persistent, or recurrent disease on or after 2 systemic therapies.
21. Aldesleukin	Treatment of adults with metastatic melanoma.
22. Peginterferon alfa-2b	Adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy.
23. Vemurafenib	Treatment of unresectable or metastatic melanoma with the *BRAF* V600E mutation as detected by an FDA-approved test.
24. Trametinib	Treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K mutations as detected by an FDA-approved test.
25. Dabrafenib	Treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E mutation as detected by an FDA-approved test.
26. Trametinib + dabrafenib	Indication 1: Treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K mutations as detected by an FDA-approved test. This indication is based on the demonstration of durable response rate. Improvement in disease-related symptoms or overall survival has not been demonstrated for trametinib in combination with dabrafenib.
27. Trametinib + dabrafenib	Indication 2: Adjuvant treatment of patients with melanoma with *BRAF* V600E or V600K mutations as detected by an FDA-approved test, and involvement of lymph node(s), after complete resection.
28. Pembrolizumab	Indication 1: Treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if *BRAF* V600 mutation positive, a *BRAF* inhibitor.
29. Pembrolizumab	Indication 2: Treatment of patients with unresectable or metastatic melanoma.
30. Pembrolizumab	Indication 3: Treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.
31. Nivolumab	Indication 1: Treatment of patients with unresectable or metastatic melanoma and disease progression after ipilimumab and, if *BRAF* V600 mutation positive, a *BRAF* inhibitor.
32. Nivolumab	Indication 2: Adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.
33. Nivolumab + ipilimumab	Treatment of patients with *BRAF* V600 wild-type, unresectable, or metastatic melanoma.
34. Talimogene laherparepvec	Indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.
35. Cobimetinib	For the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K mutation, in combination with vemurafenib. Cobimetinib is not indicated for treatment of patients with wild-type *BRAF* melanoma.
36. Avelumab	Treatment of adults and pediatric patients 12 years old and older with metastatic Merkel cell carcinoma.

Continued

Table II. Cont'd

Drug	Treatment
37. Encorafenib + binimetinib	Treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation, as detected by an FDA-approved test.
Other	
1. Mafenide acetate solution	For use as an adjunctive topical antimicrobial agent to control bacterial infection when used under moist dressings over meshed autografts on excised burn wounds.
2. Propranolol	Treatment of proliferating infantile hemangioma requiring systemic therapy.

FDA, Food and Drug Administration; *MPS*, mucopolysaccharidosis.
*Some drugs received approval for more than 1 dermatologic orphan indication. In such cases, the drug name appears again in this list, along with a numbered indication.

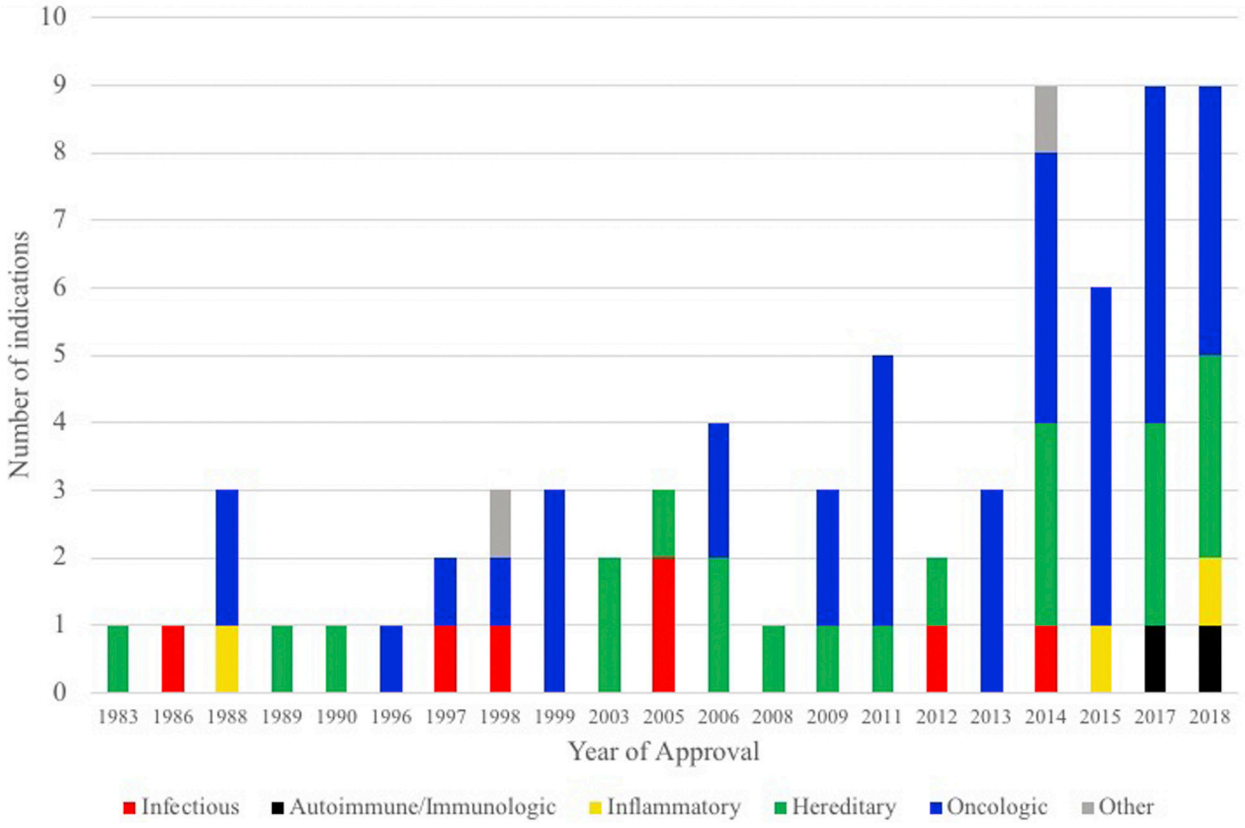

Fig 2. Orphan indications approved to treat skin conditions and skin-related cancers, by disease category.

1997 and the Pediatric Research Equity Act of 2003 has effectively stimulated the growth of pediatric drug labels.[37-40] The impact of these pieces of legislation on drug development for pediatric dermatologic diseases, specifically, is an area for future research.

ODA LOOPHOLES

Salami-slicing

Salami-slicing of common diseases to attain orphan status is one perceived form of gamesmanship of the ODA.[8] For example, pembrolizumab is an anti-programmed cell death protein 1 (PD1) immunotherapy approved to treat 11 different types of cancer, including melanoma.[41] A multitude of clinical trials involving pembrolizumab are underway for other cancer types and for use in combination therapies.[42] The prevalence of melanoma in the US was more than 1,200,000 individuals in 2015[43]; however, orphan drugs to treat melanoma apply to a narrow subset of the cancer, often metastatic disease, thus allowing the indication to fall within the 200,000-person prevalence threshold of the ODA. An indication is often winnowed even further

based on specific genetic variants, such as the V600E or V600K mutations. As of December 31, 2018, pembrolizumab had 3 approved dermatologic orphan indications and 4 additional orphan indications for nondermatologic cancers.[22] Of note, pembrolizumab is widely regarded as a "blockbuster" drug, with sales exceeding $2 billion in the fourth-quarter of 2018 alone.[44]

Mass-market drug repurposing

Repurposed orphan drugs are mass-market drugs that later gain approval for orphan indications. These drugs are sometimes referred to as "partial orphans" to recognize that they have both orphan and nonorphan uses.[8,45] For example, adalimumab, which currently holds the position of top-selling pharmaceutical drug worldwide,[46] was first approved for the treatment of rheumatoid arthritis in 2002 and later gained approval as an orphan drug for hidradenitis suppurativa (HS) in 2015. FDA-approved biosimilars to adalimumab do not have indications on-label for treatment of HS because orphan market exclusivity shields adalimumab from competition for this particular indication through 2022 in adults and 2025 in a pediatric population. Kaiser Health News reported in 2017 that more than 70 orphan drugs were first approved for the mass market.[8] Repurposing has implications for a drug's profitability because a repurposed drug can derive revenue from both orphan and nonorphan sales. Adalimumab, for example, derived approximately 4% of its $13.6 billion in total sales revenue from orphan indications in 2016.[45]

Market exclusivity prolongation

The ability of orphan exclusivity to extend beyond the patent term when exclusivity additively accrues from multiple orphan indications is another cause for concern.[20] The relationship between the total duration of orphan exclusivity vs patent life for pharmaceutical drugs is an area ripe for further research.

PROPOSED REFORMS

Elimination of the prevalence-based definition of orphan status and replacement with a definition based on commercial nonviability could reduce the ability of drug companies to profit excessively from orphan drug approvals by making orphan status contingent on adequate evidence that a drug is not expected to be commercially profitable.[47] Measures to curb excessive profits are justifiable in light of the fact that a sizeable proportion of orphan drugs and scientifically "novel" drugs are discovered in a university setting, funded by taxpayer dollars.[48]

To limit the benefits of salami-slicing, the FDA could require, for any given drug, that all subsequent orphan indications assume the exclusivity end date of the first approved orphan indication (ie, 1 orphan drug, 1 exclusivity end date). Similarly, the FDA could bar repurposed drugs from receiving orphan market exclusivity on the grounds that these drugs are not true additions to the therapeutic arsenal and have revenue streams from nonorphan indications. A potential downside to the above-mentioned reforms is that they disincentive drug companies from seeking FDA approval for secondary orphan indications. Although providers can prescribe off-label for nonapproved uses, FDA approval generally benefits patients vis-à-vis insurance coverage and access to dermatologic therapies.[49]

THE FUTURE OF DERMATOLOGIC DRUG DEVELOPMENT

In keeping with scientific advancements and market trends, we forecast a growth in nucleotide-based therapies, including gene therapy, antisense oligonucleotides, and small interfering RNA, an increase in orphan approvals for biomarker-derived subsets, and a steady movement of large pharmaceutical companies into the rare disease space. Nucleotide-based therapies may disrupt the drug development bent toward orphan anticancer drugs as large companies seek to develop or acquire rights to new curative gene therapies for exceedingly rare nononcologic disorders.[50] Academic institutions play an increasingly critical role in drug development, delineating biologic changes that can become new drug therapies, repurposing existing drugs for new indications, and developing therapies for ultra-rare conditions often ignored by industry. Continued growth of academic–industry partnerships can accelerate the translation of novel drug targets into FDA-approved therapies.[51] Finally, the role of the skin microbiome in skin disease has attracted interest within the dermatologic community, and metagenomic profiling of skin microbial communities may provide a basis for novel diagnostic tests and therapies.[52-55] This is an exciting new frontier that holds promise in treating various dermatologic conditions in the future.

CONCLUSION

In sum, the past 35 years has yielded 72 approved orphan indications for dermatologic conditions. Anticancer treatments represent a large proportion of all approvals and likely will continue to do so in the near term. A reformed system of orphan incentives can curb misuse of the ODA and help

achieve more affordable drug prices while retaining its force as a stimulus of innovation.

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