The Food and Drug Administration's Role in Dermatologic Drug Development

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KEYWORDS

• Dermatology • Drug development • Food and Drug Administration • Investigational New Drug • New Drug Application

KEY POINTS

- The mission of the Food and Drug Administration (FDA) is to ensure the safety and effectiveness of dermatologic drugs, as authorized by the Federal Food, Drug, and Cosmetic Act (FD&CA) and regulated by Title 21, Code of Federal Regulations (CFR).
- Unlike federal regulations, FDA guidance for industry reflect the Agency's current thinking on a topic and are not legally binding on drug sponsors or the FDA.
- Because drug development is continually evolving, the Division of Dermatology and Dentistry (DDD) in the Center of Drug Evaluation and Research (CDER) actively encourages dermatologic drug development by regularly engaging with sponsors and other stakeholders.
- The primary basis for FDA approval of a drug marketing application is the benefit-risk assessment.

INTRODUCTION

The process of discovering and bringing any new molecular entity (NME) to market is one that requires persistence, significant financial resources, and a broad horizon. Although pharmaceutical companies may carry the immediate burden of investing money and time, there are other major stakeholders in drug development including the Food and Drug Administration (FDA), researchers, patients, prescribers, and payers. Each group has obligations, priorities, and influences that shape their behavior (**Table 1**).

These relationships are complex. There is an inherent tension when the FDA and pharmaceutical companies, the stakeholders most actively involved in drug development, have different perspectives and motivations, which can result in competing messages to researchers, patients, patient advocacy organizations, prescribers, and payers. These stakeholders have their own agendas and perceptions and seek to influence the FDA and pharmaceutical industry. Nonetheless, all share a common goal—delivering safe and effective drugs to dermatologic patients.

Certain factors influence stakeholder decisions about the development of dermatologic drugs (**Box 1**). The first two, scientific understanding of the pathophysiology of dermatologic conditions and genomic sequencing and its application to dermatologic conditions, significantly influence researchers and pharmaceutical companies in the

Authors' Note: While the authors are employees of the US Food and Drug Administration, the opinions and views expressed in this article are their own and do not reflect US Food and Drug Administration policy or official guidance.

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Abbreviations

IND	Investigational New Drug
NDA	New Drug Application
BLA	Biologic License Application
FDA	Food and Drug Administration
CDER	Center for Drug Evaluation and Research
DDD	Division of Dermatology and Dentistry
NME	new molecular entity
GCP	good clinical practice
FD&CA	Food, Drug, and Cosmetic Act
CFR	Code of Federal Regulation
PDUFA	Prescription Drug User Fee Act
PREA	Pediatric Research Equity Act
REMS	Risk Evaluation and Mitigation Strategy
MUsT	maximal usage trial
PK	pharmokinetic
PMR	postmarketing requirement
PMC	postmarketing commitment
BSA	body surface area
CMC	chemistry, manufacturing, and controls
USC	United States Code
BRA	benefit-risk assessment
EOP2	End-of-Phase 2

process of drug discovery. "Medical necessity," a payer term that originated in the 1940s with private insurance and adopted by Medicare and Medicaid, was borne out of a need to justify insurance coverage, but was largely left to a physician's discretion as to what patient care was "appropriate and effective" to diagnose and treat a medical condition.[19] As the cost of health care and patient demands increased, administrators introduced "cost-effectiveness" as a value-based consideration for coverage in the 1970s, requiring comparisons of "necessity" between medical conditions and treatments. The Social Security Act defined "medical necessity" for Medicare in terms of morbidity and mortality and excluding what was "not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."[20] As a result, population-level practice standards superseded professional medical judgment of individual physicians (and the patient) in the determination of necessity for patient care. A likely unintended consequence of this approach was the creation of a hierarchy of medical needs that established dermatologic conditions as relatively benign since the most common dermatologic conditions do not result directly in death or chronic and progressive physical dysfunction. In addition, because the most familiar dermatologic conditions may seem to improve over time or patients do not seek medical care, the number of affected dermatologic patients is frequently underestimated. The effect has been to minimize the importance of treatment of dermatologic conditions, stunting the development of most dermatologic drugs,[21] with the notable exception of those used to treat metastatic melanoma. Lastly, one of the primary challenges affecting the design of clinical trials of dermatologic drugs has been the lack of efficacy endpoints that adequately and reliably assess subjective aspects (such as itch or pain) of a dermatologic condition that may provide a clinically meaningful benefit to a patient, even without objective improvement of their skin disease.

Despite the complexities and challenges in this environment, the FDA approved 46 NMEs for dermatologic indications from 2011 to 2022, 27 of these within the Division of Dermatology and Dentistry (DDD), the division in the CDER responsible for regulating dermatologic drugs in development and seeking approval for marketing (Appendix 1). Among these are apremilast (2014), a novel oral therapy for psoriatic arthritis and psoriasis; clascoterone cream 1% (2020), a first-in-class treatment of acne; and afamelanotide (2019), the first FDA-approved drug to increase pain-free light exposure in patients with the rare disease erythropoietic protoporphyria (EPP).

Table 1
Key stakeholders in drug development

Stakeholder	Obligations	Priorities	Influences
FDA[1,2] (CDER and DDD)	Ensuring that approved drugs are safe and effective	Favorable drug benefit-risk assessment supported by scientific rigor Drug quality Patient and prescriber education	Public perception Communication of benefit vs risk Federal funding
Pharmaceutical companies[3–5]	Profit for investors	Market size (number of patients affected) Market exclusivity Trial efficiency Probability of success Return on investment	Research & development costs Risk tolerance of investors Regulation (FDA and environmental) Market competition Formulary tiers Public perception
Researchers (including academia and scientists)[6–8]	Advance scientific understanding of dermatologic disease	Discovery of target to solve medical problem Characterization of target molecule	Scientific and technological advances Financial resources Patient advocacy organizations Employer priorities Personal research interests
Prescribers[8–10]	Providing optimal care for their patients	Drug safety and effectiveness Drug access/availability Identifying gaps/ medical need	FDA approval of drugs Drug/health literacy Time constraints Clinical guidelines Formularies Pharmaceutical reps Patient demands
Patients[11–14]	Define clinically meaningful impacts	Drug safety and effectiveness Quality of life	Drug/health literacy Prescriber decisions Competing "experts" Direct-to-consumer advertising Drug access/cost Insurance coverage
Patient advocacy organizations (PAOs)[15–17]	Engage with decision-makers on behalf of patients with dermatologic conditions	Increase funding for disease research and treatment Educate and support patients and public Greater visibility for constituents	Donors (often pharma) Researchers
Payors (public)[18]	Efficient budget management	Size of budget relative to population supported	Cost of health care Determinations of medical necessity Competing government budget priorities
Payors (private)[13]	Profit for investors	Favorable drug benefit-cost assessment	Cost of health care Determinations of medical necessity Optimizing beneficiary mix

Abbreviations: CDER, Center for Drug Evaluation and Research; DDD, Division of Dermatology and Dentistry; FDA, Food and Drug Administration.

Box 1
Factors influencing decisions about dermatologic drug development

Scientific understanding of pathophysiology of dermatologic conditions

Genomic sequencing and its application to dermatologic conditions

Considerations of dermatologic conditions as "medical" vs "cosmetic"

Perceptions about "seriousness" of dermatologic conditions relative to other medical conditions (such as cancer)

Size of patient population affected by dermatologic conditions compared with other medical conditions (such as heart disease or diabetes)

Availability of instruments to measure clinically meaningful but subjective components of a dermatologic condition in an objective and consistent method to demonstrate effectiveness

CDER continues to support expanding the availability of drugs to treat rare diseases through the Rare Diseases Program[22] and incorporating patient perspectives through the "Patient-Focused Drug Development"[23] initiative in accordance with the 21st Century Cures Act and the FDA Reauthorization Act of 2017. Forums for gathering input from stakeholders have included FDA-led meetings (e.g., for alopecia areata in 2017[24]) and patient listening sessions (eg, a patient-led session on Gorlin Syndrome[25]).

Within the context of the regulatory framework that governs the interactions of DDD and the pharmaceutical companies who sponsor investigational drugs during the drug development process, we will discuss how the FDA's policies and practices have continued to evolve to incorporate scientific advances and to facilitate approval for drugs in a timely manner for a broad spectrum of patients. We will provide several examples to highlight areas where DDD found common ground with stakeholders to increase the therapeutic options for dermatologic patients while still maintaining regulatory standards required for approval.

THE REGULATORY FRAMEWORK

The 1962 Kefauver-Harris Drug Amendments of the Federal Food, Drug, and Cosmetic Act (FD&CA)[26] provides the legal basis for the FDA mandate to ensure "the safety, effectiveness, and reliability of drugs."[27] The strategic framework for new drug development and approval is further outlined by regulation in Title 21 section 355 of the US Code (USC)[28] and sections 312 and 314 of the Code of Federal Regulations (CFR).[29] These regulations delineate the distinct roles of the sponsor and the FDA. The sponsor is primarily responsible for "managing the overall development of their drugs…, determining the nature and timing of regulatory submissions…, soliciting input and guidance from the FDA…, and providing well-organized and complete…submissions…to the FDA for review."[30] Meanwhile, the FDA must ensure the safety and rights of subjects at all phases of development; during Phases 2 and 3, "ensure that the quality of the scientific evaluation…is adequate to permit the evaluation of the drug's effectiveness and safety"[31]; enforce good clinical practice (GCP) and human subject protections (HSP) requirements; review submissions; and take regulatory actions as necessary.

A drug or biologic that is being studied in human subjects is known as an Investigational New Drug (IND). When the sponsor of the drug believes there is sufficient evidence for approval, the company submits a New Drug Application (NDA) for drugs or Biologic License Application (BLA) for biologics[1] with the goal of obtaining approval to market the product in the USA. From the FDA perspective, drug development can be broken down into four stages: *pre-IND*, *IND*, *NDA/BLA*, and *postmarketing*.

The general process and requirements for the different phases of drug development are outlined in 21 CFR 312.21,[32] although there is room for operational interpretation by the FDA. Broadly, the FDA communicates their interpretation and current thinking on topics that apply across the Agency in the form of Guidances for Industry.[33] Individual guidances, which may be updated as science and technology evolve around drug development, provide sponsors more specific details about the FDA's current intent and expectations to ensure standards are met, with the goal of a more consistent and transparent review and approval process. To be clear though, unlike the requirements set out in regulations, guidances are not legally binding on sponsors *or* the FDA. Guidances serve as "rules of the road" but the development process for each molecular entity will be unique.

[1]For the purposes of this article, biologics (generally defined as large complex molecules produced through biotechnology in a living system) follow a similar process as drugs (small chemically-synthesized molecules) in DDD.

For this reason, there are formal meeting opportunities available during the review and approval process for a sponsor to engage and communicate with DDD. The purpose and structure of these meetings are laid out in Prescription Drug User Fee Act (PDUFA) V and 21 CFR 312.47,[34] with more detail provided in the FDA documents listed in Appendix 2. These meetings are highly recommended because they are beneficial for both the sponsor and DDD, but they are not mandatory and should be initiated/requested by the sponsor. Formal meetings allow for greater transparency between the sponsor and DDD about the development program of a specific drug; however, they are purposefully narrow in focus. Before the meeting, sponsors submit background materials and specific questions about the structural aspects of the program for which they are seeking feedback and/or agreement from the FDA. For example, if a sponsor wishes to deviate from the generally accepted guidance documents or has developed a novel trial design, a meeting is the ideal opportunity to introduce and discuss these proposals with DDD.

In the sections about the drug development stages that follow, we'll first review the regulatory requirements and discuss the recommended formal meeting(s) with FDA. The list of the most applicable FDA guidances for that stage of drug development is available in Appendix 2. Finally, we'll provide an example of a recently-approved dermatologic drug reviewed in DDD that used a process or guidance to facilitate the progress at that stage of the drug's development program.

Pre-Investigational New Drug Stage

Regulation

It is well-known that pharmaceutical companies invest significant resources to discover new molecular entities (NME) that have the potential to treat human diseases. Before testing drugs in humans, pharmaceutical companies must first establish the properties of an NME (also known as characterization), as well as conduct multiple nonclinical pharmacology and toxicology tests (**Box 2**) to establish baseline knowledge about its potential for toxicity in humans. The results of these tests are used to estimate a safe first-in-human (FIH) starting and maximum exploratory doses, identify organ targets and adverse effects to establish safety monitoring requirements, and predict risk for special populations (pregnancy, pediatrics), among others.

Box 2
Typical nonclinical tests conducted in the pre-IND/early IND stage for dermatology drugs[35]

- Pharmacokinetics (absorption, distribution, metabolism, and excretion, ADME)
- Pharmacodynamics (mechanism(s) of action)
- Acute, subacute, and chronic toxicity (single- and repeat-dose)
- Determination of first-in-human dose and no observed adverse effect level (NOAEL)
- Genotoxicity
- Reproduction toxicity
- Developmental toxicity
- Carcinogenicity
- Local tolerance studies
- Immunotoxicity
- Photosafety

When the sponsor determines that the drug has been sufficiently characterized and demonstrated potential to treat a particular condition based on these tests, the sponsor can seek feedback from the FDA about their development program during a pre-IND meeting. Issues that might be covered during this meeting include safety issues related to the proper identification, strength, quality, purity, or potency of the investigational drug[36]; animal studies conducted to support human testing; preliminary evaluation of a Phase 1 trial design; and adequacy of the preclinical program to support the initiation of an IND.[37]

DDD and dermal safety studies

Because a number of dermatologic drugs are applied topically, dermal safety studies have been traditionally initiated during the pre-IND phase in animal models and then later in healthy human volunteers[2] to evaluate for local skin reactions such as irritation, contact sensitization, phototoxicity, and photoallergenicity at the site of application. However, there have been concerns about the limitations and the broad applicability of these tests to actual clinical use. For example, dermal safety studies in animals can be complicated by grooming habits that result in the

[2]Dermal safety studies are done later when the final to-be-marketed formulation has been determined. In early clinical development, human studies on dermal safety may be done for selection of vehicle or strength of the active ingredient.

ingestion of the drug and increased toxicity or restrictive banding to keep patches in place causing hepatonecrosis.[38] Dermal safety evaluations in humans in the early stages of development are performed on the normal skin of healthy subjects (not on lesional skin of patients) and under occlusion (applied as a patch), conditions not reflective of real-life use for topical drug products. There are also ethical concerns about induction and potential permanence of unnecessary contact sensitization. Generally, the results of these tests haven't been incorporated into the labeling of topical drug products.

Review of data accumulated over years with this approach indicated that results generated from these human dermal safety studies provide information on the potential of the topical drug product to elicit each relevant dermal toxicity but may not accurately convey the actual risk from clinical use. DDD convened a public workshop of FDA scientists along with representatives from the pharmaceutical industry and other stakeholders in September 2018 to discuss these concerns.[39] The consensus that certain dedicated dermal safety studies may not be necessary across the board if the assessment is conducted during Phase 3 trials led to a draft guidance, *Contact Dermatitis from Topical Drug Products for Cutaneous Application: Human Safety Assessment*.[40]

DDD's activities coincided with a larger FDA effort to support and incorporate advances in science and technology, broadly called new approach methodologies (NAMs), during nonclinical drug development.[41] Led by CDER toxicologists, the FDA produced a Predictive Toxicology Roadmap[42] and formed the Alternative Methods Working Group,[43] to identify, introduce, and test NAMs that could ultimately replace animal models. With the application of pharmacogenomics and proteomics, the goal is that NAMs using in vitro, in chemico, and in silico testing, will be shown to be more predictive of human toxicities and outcomes and improve regulatory efficiency. For pharmaceutical companies, such testing strategies have the potential to enhance drug discovery and expedite drug development. If a sponsor is considering using a NAM to derive or supplement nonclinical data to support clinical studies, the pre-IND meeting is an ideal forum to provide DDD details about the methodology, demonstrate that it is appropriate for use, and gain FDA feedback on its acceptability.

Investigational New Drug Stage

Regulation

Investigational new drugs can only be tested in humans in clinical trials in the United States under an IND. An NME will go through the traditional pathway which consists of a sequence of three increasingly stringent phases: Phase 1, FIH studies, often conducted with a small number of healthy subjects to gather information about pharmacokinetics, toxicities, adverse events, and dosing; Phase 2 proof-of-concept efficacy studies and dose-finding studies in affected subjects; and Phase 3 studies with larger numbers of affected subjects to confirm the efficacy and further describe the safety profile of the drug. With some drugs, a company may choose to conduct Phase 1 or 2 studies outside of the United States.[44] A key milestone meeting during the IND stage is the End-of-Phase 2 (EOP2) meeting.[3] Some topics for consideration are the Phase 3 trial design(s) including dose selection, endpoint selection, and the number of subjects needed to provide an adequate efficacy and safety database; pediatric studies, including those required under the Pediatric Research Equity Act (PREA); the adequacy of the supporting nonclinical and clinical pharmacology data; and any additional information needed to support an NDA/BLA submission.[37] A Type C development meeting is appropriate for requesting feedback on other aspects of development and can be requested at any stage of IND development.

Maximal usage studies for topical products

A common strategy for treating dermatologic conditions is the use of topical products. There are multiple advantages to topical therapy compared with drugs taken orally or administered by injection. The primary advantage is that the drug is directly delivered to the target area (avoiding first-pass metabolism), and with the goal to produce less systemic exposure. Thus, topical application decreases the possibility of drug–drug interaction and potential toxicity to other organs. Several factors intrinsic to the patient and disease can impact topical drug absorption to the degree that systemic exposure (and increased risk of off-target adverse reactions) becomes a concern. The possibility of systemic absorption increases when the topical drug is applied to thin-skinned areas (eg, face or intertriginous areas) or the skin barrier is compromised due to the pathophysiology of the disease (eg, a psoriatic plaque) or symptoms (eg, intense pruritus leading to

[3]For drugs that are in expedited review programs, this meeting may take place at the End of Phase 1.

scratching). Other variables that increase the risk of systemic absorption include application to larger body surface area and increased frequency and/or duration of application. For pediatric and geriatric populations, there are additional factors to consider. Neonates and infants have a higher rate of percutaneous absorption due to a larger ratio of total body surface area (BSA) to body mass compared with adults, greater perfusion in the subcutaneous layer, and more immature drug-metabolizing structures.[45] Skin atrophy occurs with aging and excessive lifetime sun exposure, putting geriatric patients at increased risk for systemic adverse reactions, which can be compounded if the patient also has decreased organ function, takes other systemic medications, or has significant comorbidities.[46] The most familiar example of this phenomenon is the development of hypothalamic–pituitary–adrenal (HPA) axis suppression with topical corticosteroid use, with the greatest potential occurring in infants due to their high ratio of total BSA to body mass.[47]

To characterize the greatest degree of systemic absorption for a topical drug, a sponsor will typically conduct a maximal usage trial (MUsT, also known as a maximal use pharmokinetic trial) during the IND stage after the expected dosing regimen for the drug's indication has been selected, typically during Phase 2 trials. With the expectation that the highest risk of systemic absorption will occur when a patient applies the maximal amount prescribed according to the proposed labeling, the parameters of a MUsT design are required to reflect the conditions in which maximal application is anticipated, including the total amount of affected BSA treated in a single application, with the application of the highest proposed strength at the maximum anticipated frequency, and for a duration sufficient to achieve maximal drug absorption. In addition, the MUsT population should reflect the expected demographics of the target population(s) that are at greatest risk for systemic absorption—typically children, elderly, and those with greater disease severity.[48] The results of the MUsT may be used in different ways. For a topical formulation of an established systemic drug, the pharmokinetic (PK) results may be compared with those of the PK curve of the predetermined reference drug, to inform the understanding of relative risk of systemic adverse reactions and inform labeling decisions.[4] For drugs with a hormonal component, subjects are evaluated for HPA axis suppression, which may influence the benefit-risk assessment, particularly for younger patients. For NMEs, the MUsT may establish reference PK levels of systemic absorption for the drug. Examples of recently-approved dermatologic drugs whereby a MUsT was required as an element of the drug development program include minocycline 4% foam for acne (2019),[49] minocycline 1.5% foam for rosacea (2020),[50] tirbanibulin 1% ointment for actinic keratoses (2020),[51] and clascoterone 1% cream for acne (2020).[52] In the clascoterone MUsT, the increased incidence of HPA suppression in the subset of subjects aged 9 to 11 years was a contributing factor in limiting FDA approval of this drug to acne patients 12 years and older.[53]

New Drug Application/Biologic License Application Stage

Regulation

The *NDA/BLA stage* commences when a company submits to the FDA a comprehensive package[54] of the nonclinical and clinical studies conducted using the investigational drug for review and hopefully, approval for marketing. Before submission, the sponsor should request a *pre-NDA/BLA meeting*. The purpose of this meeting is to review the scope of the drug development program to ensure that there is sufficient evidence to enable DDD to make an informed assessment of the drug's efficacy and safety, and that there are no gaps in data. In addition, agreement should be reached on administrative details such as the order of contents, formats, or presentation of data. Preliminary discussions of risk management plans or postmarketing studies may also take place.[37]

Central to the submission of a marketing application is the requirement of demonstrating effectiveness, or "substantial evidence" that a product has an impact on the way a patient feels, functions, or survives. The 1997 FDA Modernization Act (FDAMA), codified in 21 USC 355, provides the statutory definition for "substantial evidence" of effectiveness that companies must demonstrate in order for a drug to be approved:

> …evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved… that the drug will have the effect it purports …to have under

[4]If the threshold level of systemic absorption for the reference drug that is necessary to cause an adverse reaction is unknown, those potential adverse reactions are included in the prescribing information for the topical drug, even if the PK levels are lower than the systemic drug.

Table 2
The FDA benefit-risk framework for human drug review[58]

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk and Risk Management		
Conclusions Regarding Benefit-Risk		

> the conditions of use prescribed, recommended, or suggested in the labeling…[55]

Other requirements in the application necessary to assess the safety and reliability/product quality include a summary of safety information gained from clinical trials and a summary of chemistry, manufacturing, and controls (CMC). For biologics, immunogenicity studies are also included.

For a "standard" review, the DDD review team has 12 months from the date of submission to thoroughly review the NDA/BLA.[56] During the first 60 days, the team reviews the contents and quality of the sponsor's application for adequacy, consistent with the agreements made during the pre-NDA/BLA meeting. If the application is in order, it will be officially accepted ("filed") for review. Over the remaining 10 months, the members of the DDD team will individually perform analyses of the data to make their own determinations about the drug's efficacy and safety to ensure consistency with the sponsor's results, review quality control and manufacturing processes, conduct study and manufacturing site inspections, and identify any areas of uncertainty about any aspect of the drug. If questions arise during the DDD review, information requests (IRs) may be sent to the sponsor. The review team meets collectively at designated meetings during the review to share their findings with the group, discuss concerns, and build consensus about the overall benefit-risk assessment (BRA) and labeling of the drug at the proposed dose and indication.

The benefit-risk assessment framework[57] (**Table 2**) integrates the analysis of all the reviewers on the DDD team—clinical pharmacology, pharmacology and toxicology, CMC, biostatistics, and clinical—to provide a comprehensive evaluation of the evidence of clinical benefit to the target population, risks related to adverse reactions and product quality, and areas of uncertainty in the larger context of the seriousness or rarity of the disease and the extent of treatments available. If the BRA is favorable and approval recommended, the team will then focus on the communication of this information to the patient and prescriber in the product labeling information.

Approval of the marketing application signifies that the FDA has determined that "the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling."[59] If the review process reveals significant deficiencies in any of these areas, a Complete Response Letter (CRL) will be sent to the sponsor to explain why the statutory standards were not met, along with the elements required to resolve any deficiencies.[60] A CRL does not preclude future resubmission of the marketing application; however, the sponsor is strongly encouraged to request a meeting with the review team to clarify FDA expectations and discuss remediation.

Demonstrating substantial effectiveness in a rare disease

In 1983, Congress passed the Orphan Drug Act[61] to incentivize pharmaceutical companies to develop drugs for rare diseases, defined as one that affects less than 200,000 people in the US,[62] because most of these conditions do not have FDA-approved treatments. In addition, many of the 7000+ rare diseases are life-threatening and/or affect pediatric populations. For pharmaceutical companies, the small market size alone might discourage investment. There are also unique barriers to drug development for these small populations compared with more common dermatologic conditions, including greater uncertainty about the natural history and pathophysiology of the disease which can affect the development of appropriate inclusion criteria for subjects, trial design, and efficacy endpoints.[63] As noted earlier, the purpose of the FDA's Rare Disease Program is to raise the visibility and encourage the development of drugs for such conditions. Without specific treatments, clinicians often turn to off-label use of drugs that have not been tested in these patients, which may or may not have activity for the

condition and may lead to unexpected adverse reactions.

Erythropoietic protoporphyria (EPP) is a rare genetic condition caused by a deficiency in ferrochelatase, the final enzyme in the heme synthesis pathway, leading to an accumulation of protoporphyrin IX (PPIX) in the skin, as well as in red blood cells and plasma. Clinically, this condition presents in childhood, when the affected patient experiences an immediate and severe phototoxic reaction when their skin is exposed to UVA sunlight (380–420 nm). Without treatment, the primary management strategy is sun avoidance, to include staying indoors in windowless rooms, sun-protective clothing, sunscreen, and over-the-counter antioxidants such as beta-carotene.

Afamelanotide, an α-melanocyte-stimulating hormone, which binds to the melanocortin-1 receptor (MC1R) which induces melanin synthesis and enhances DNA repair processes, was identified as a potential treatment of EPP. Clinically, the effect is to produce darkening of the skin, that is, stimulated photoprotection to better tolerate UV light. Because EPP is a rare disease, the sponsor requested and was granted several FDA statuses for afamelanotide to facilitate its development: orphan drug designation in 2008 and Fast Track designation in 2016. Early in the IND stage, the sponsor met several times with the FDA, including an EOP2 meeting in 2015, to discuss several issues unique to drugs being studied for rare diseases. Without the precedent of an approved treatment, novel endpoints need to be developed and validated for drugs. After the evaluation of the Phase 2 trial results, the sponsor and FDA agreed on an endpoint of "duration of direct sunlight exposure between [the hours of greatest intensity] on days when no pain was experienced" that was clinically meaningful,[64] but one that differed from the endpoint used in the Phase 2 trials.

A typical challenge for rare diseases is the small population of affected patients eligible to participate in clinical trials. For the afamelanotide Phase 3 trial, the sponsor could only enroll 94 EPP subjects. The FDA agreed that the results of this single Phase 3 pivotal trial, if favorable, along with supportive data from other clinical trials, would provide an adequate database for efficacy and safety. While the Phase 2 studies could not be considered "adequate and well-controlled" trials due to the post hoc change in the primary endpoint, the results could be supportive.[65] Ultimately, with the effect of afamelanotide increasing the duration of pain-free sun exposure in EPP subjects, the DDD consensus was that the evidence from the Phase 2 and 3 trials taken together was sufficient to demonstrate efficacy with an acceptable safety profile. Thus, afamelanotide was approved as a first-time treatment of EPP.

The benefit-risk assessment and communication and mitigation of risk

As previously mentioned, the decision of whether or not to recommend a dermatologic drug or biologic for approval rests on the integrated BRA of the DDD review team. Although the FDA framework provides a more structured and systematic approach to integrating the quantitative evidence, the BRA is largely qualitative,[66] and members of the review team may have different perspectives on the risks and benefits of a drug. It is not unusual for the review team to seek other perspectives within DDD or through consultation with other offices within CDER or other centers when there is overlapping jurisdiction. Occasionally, an issue during an IND or NDA/BLA review that could potentially affect or be impacted by FDA medical policy will be brought to the CDER Medical Policy and Program Council for senior management input, particularly if it involves class-level safety concerns or takes a position that might be precedent-setting, thus ensuring consistent implementation of policy.[67]

The Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC), composed primarily of impartial medical specialists, typically physicians, is another source of expert opinion. In 2016, a unique safety concern of suicidal ideation and behavior (SIB) was identified during the drug development program of brodalumab, an interleukin-17 receptor A (IL-17A) blocker proposed for the treatment of moderate to severe psoriasis. While no causal association could be established between brodalumab and SIB, it was nonetheless troubling and the number of events occurring during development could not be dismissed. Considerable debate among the DDD review team occurred about how to weigh this adverse event into the benefit-risk assessment and the approval decision, especially in light of strong evidence of brodalumab's effectiveness and the recognized need to provide treatment alternatives for patients with moderate to severe psoriasis. It was noted that no psoriasis treatment is "universally effective for all patients and most severely affected patients generally lose response to the products they use over time."[68] To obtain additional perspectives and "independent expert advice that contributes to the quality of the agency's regulatory decision-making and lends credibility to the product review process,"[69] DDD brought these questions to the DODAC. The DODAC ultimately recommended approval of the biologic with the additional recommendations for

prominent disclosure of these safety findings and a post-marketing risk management program. These recommendations from the DODAC, in addition to those from the Risk Evaluation and Mitigation Strategy (REMS) Oversight Committee, factored significantly into the decision to approve brodalumab as a second-line therapy for adult patients with moderate to severe plaque psoriasis who have failed other systemic therapies.[70]

For drugs such as brodalumab that demonstrate strong benefit but also pose an uncertain level of significant risk, gaining the support of an expert panel may not be enough to improve the benefit-risk balance. The primary means to tangibly improve the BRA is through risk mitigation. The prescribing information (PI, also known as labeling information) is the FDA's most visible method of communicating the benefits and risks of a drug. Communication of a serious risk can be strengthened through a black box warning. Although sufficient for most drugs, the PI is a passive means of risk mitigation. In addition, the label information may not be adequate to provide the context of the risk as it applies to an individual. Without this context, patients may not be able to make fully informed decisions about the drugs that are prescribed to them.[71]

In the case of brodalumab and SIB, FDA approval was contingent on the sponsor's implementation of a REMS, as recommended by the DODAC and the REMS Oversight Committee. The purpose of a risk management strategy is to mitigate an observed risk, thus ensuring that the benefits of a drug outweigh its risks.[72] A REM can also provide data to the sponsor, reportable to the FDA, about the real-world incidence of the adverse event being tracked. For the brodalumab REMS, prescriber/pharmacy education and certification, patient registry with documented patient counseling and consent, and a patient wallet card are some of the elements to assure safe use (ETASU)[73] of brodalumab.

Postmarketing Stage

After a marketing application for a drug has been approved, the sponsor has several immediate responsibilities. Before distributing the drug, the applicant must submit their final versions of the label, packaging, and promotional materials for approval. Any risk management programs required by the FDA (such as the REMS program for brodalumab due to the SIB risk) are implemented when the drug is marketed. In addition, any postmarketing requirements (PMRs) required (such as deferred pediatric studies) or postmarketing commitments (PMCs) agreed on during the NDA/BLA review should be initiated. Finally, for NMEs and biologics, the applicant may request a postapproval feedback meeting with the FDA. This meeting is an opportunity to discuss the quality of the application, evaluate the communication process during drug development and marketing application review, and learn from what was successful and whereby improvement could be made in future drug programs.

Besides these immediate obligations, the applicant must continue long-term safety surveillance of the drug in accordance with 21 CFR 314.80, and submit quarterly reports of adverse events.[74] While the number of subjects enrolled in the Phase 3 trials may have been enough to detect the most common adverse reactions of a drug, long-term surveillance is necessary to monitor for less common adverse reactions. Rare adverse events may not be observed until the drug has been prescribed to a larger population or has been taken for longer periods of time. Adverse events that are serious and unexpected must be reported to the FDA in a timely manner, that is, in a 7- or 15-day safety report.

The applicant must also submit a comprehensive annual report of the drug development program to the FDA, including a status of the PMRs/PMCs, adverse events, additional nonclinical studies conducted, anticipated shortages, and future plans to study or modify aspects of the drug (e.g., manufacturing process).[75] The applicant may continue to study its efficacy in other indications and in other populations. In some cases, the nonclinical studies previously conducted during the pre-IND stage will still be applicable to these new clinical studies, shortening the developmental pathway to approval. Assuming that the drug formulation and strength/concentration do not change, the company may continue to submit additional IND studies for any phase of clinical study (1, 2, or 3), depending on what other supporting clinical studies have been completed in and outside of the United States. Applications for approval for expanded indications or for additional populations are submitted as supplemental NDAs (sNDAs) or supplemental BLAs (sBLAs).

SPECIAL TOPICS OF DERMATOLOGIC CONCERN

Protecting Children Through Research

Although 21 CFR 50 Subpart D allows for clinical investigations in children,[76] until the late 1990s clinical testing in pediatric subjects was infrequently conducted for several reasons: ethical concerns about subjecting this vulnerable population to unknown safety risks, inability for the

subjects to give informed consent, extra care necessary to ensure children can be compliant with study procedures, and the perceived lack of necessity. The consensus in the medical community was to protect children by minimizing exposure to drugs under development. Thus, only about 20% of drugs under development were studied in children.[77] However, with so few drugs approved and available for pediatric use, physicians in clinical practice had no option but to treat children like "small adults" by extrapolating in a trial-and-error fashion from adult indications and dosages.[77] Anecdotal reports of adverse reactions occurring from off-label use of drugs in children increased the visibility of this issue.

Currently, the FDA has two means to maximize clinical testing of drugs under development intended for pediatric patients. Under the 1997 Best Pharmaceuticals for Children Act (BPCA), the FDA provides an incentive of up to 6 months of additional marketing exclusivity for a drug if the sponsor voluntarily conducts studies in children. In contrast, the Pediatric Research Equity Act (PREA),[78] gives the FDA the authority to require that pediatric studies be conducted if a sponsor is seeking FDA approval with a new active ingredient, indication, dosage form, dosing regimen, or route of administration, unless a waiver or deferral has been approved. This requirement ensures that whereby appropriate and practicable, drugs are developed in appropriate formulations for children, and that accurate pediatric safety and dosing information is included in labeling.[79] During development, discussion of pediatric study plans takes place no later than the EOP2 meeting. Within 60 days after the EOP2 meeting, the sponsor must submit an initial pediatric study plan (iPSP), or at least 120 days before a Phase 3 protocol submission if there was no EOP2 meeting.[80] For systemic drugs, a sponsor may request a deferral until the postmarketing stage to first characterize a drug's safety profile in adults, or a waiver for certain age groups if there are safety concerns or if studies are highly impracticable.[79]

Compared with older systemic drugs such as methotrexate and cyclosporine that have long been prescribed to treat severe dermatologic diseases such as psoriasis and atopic dermatitis, biologics have revolutionized treatment by offering rapid improvement with relatively few adverse reactions by selectively targeting aberrant proteins in specific inflammatory pathways. One of the first biologics to treat plaque psoriasis, etanercept, was first approved for adults in 2004. Although it was the first biologic approved for adolescents with psoriasis, that approval took more than 12 years due to early uncertainties related to potential drug-induced malignancy in children with long-term use. Similar safety concerns also sidetracked the study of adalimumab for pediatric psoriasis. Nonetheless, due to the significant unmet need for effective systemic therapies to treat severe skin disease in children and an ethical evolution that "the best way to bolster outcomes and protect children is through research, not from research,"[81] DDD now encourages the conduct of pediatric clinical studies earlier during the development of drugs that treat chronic dermatologic conditions affecting children. This change is most evident with the approval dates of the biologics, with a significant reduction in the time interval between approval dates for adults and those for children (**Table 3**). DDD has also authored several guidances for specific pediatric diseases to improve the transparency about FDA

Table 3
Time interval between adult and pediatric approvals for biologics used in dermatology[82]

Biologic	Indication	FDA approval Date for Adults	FDA Approval Date(s) for Pediatrics[a]	Time Interval Between Adult and Pediatric Approval(s)
Etanercept	Plaque psoriasis	Apr 2004	Nov 2016: 4–17 y	12 years, 7 months
Adalimumab	Plaque psoriasis	Jan 2008	Not FDA-approved	N/A
Ustekinumab	Plaque psoriasis	Sep 2009	Oct 2017: 12 to <17 y Jul 2020: 6 to <12 y	6 years, 1 month 8 years, 9 month
Adalimumab	Hidradenitis suppurativa	Sep 2015	Oct 2018: 12 to <17 y	3 years, 1 month
Ixekizumab	Plaque psoriasis	Mar 2016	Mar 2020: 6 to <17 y	4 years
Dupilumab	Atopic dermatitis	Mar 2017	Mar 2019: 12 to<17 y May 2020: 6 to <12 y	2 years 3 years, 2 months

[a] These dates refer only to the specified indication.

expectations about pediatric clinical trials and encourage sponsors to develop drugs for these indications (see Appendix 2).

Biosimilars

Due to the complexity of their structures and multiple indications which necessitate multiple patents, biologics enjoy a patent exclusivity period of at least 12 years, which can be extended through approval for additional indications and other minor modifications. With the expiration of the core US patents for etanercept, adalimumab, and ustekinumab approaching, biosimilars have become a rapidly expanding category of medical products coming under review in DDD. Although biosimilars have a phased development program and marketing application process described in 42 U.S C. 262 that is loosely analogous to the one for drugs and biologics, the statutory requirement for biosimilar approval is "demonstration of biosimilarity"[83] to a reference product (the branded biologic). Unlike drugs and biologics whereby the sponsor must conduct separate clinical efficacy and safety trials as evidence of effectiveness for each indication, the FDA recommends a stepwise, scientifically grounded approach to establish biosimilarity in a single indication (eg, psoriasis) through:

- Analytical comparability
- Animal studies (including toxicity)
- PK, pharmacodynamic, and immunogenicity assessments against a reference product
- Comparative clinical study with a reference product as the comparator in a single indication (e.g., psoriasis)[84]

If the FDA agrees that the sponsor has successfully demonstrated that the biosimilar is "highly similar" with "no clinically meaningful differences…in terms of safety, purity, and potency,"[83] then the sponsor may seek extrapolation to all other FDA-approved indications for the reference product, including pediatric indications, without conducting additional studies. Sponsors may not seek approval for indications that are still under exclusivity protection or make modifications to their product that go beyond what has already been established by the reference product.

SUMMARY

By virtue of its regulatory authority invested by the FD&CA, the FDA is the ultimate arbiter of drug approval in the United States, and for dermatologic drugs specifically, the Division of Dermatology and Dentistry in CDER. As a science-led organization, FDA uses the best scientific and technological information available to make benefit-risk decisions through a deliberative process. At the same time, by engaging with other stakeholders in drug development, DDD is a partner in expanding the therapeutic options for the diverse patient population affected by dermatologic conditions. We welcome frequent and open dialogue with sponsors about their drug development programs to provide timely feedback and guidance, while staying attuned to what is considered clinically meaningful to the patients who will ultimately take the drug. By constantly reassessing the parameters of risk and benefit in the context of dermatologic disease, DDD is committed to maintain the public trust in the safety and efficacy of FDA-approved drugs.

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SUPPLEMENTARY DATA

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