Dermatological Drug Development

Tomoko Maeda-Chubachi, Elizabeth Kernodle Hussey and Sylvia Furst

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“To cure sometimes, to relieve often, to comfort always.”
— Ancient Greek Epigraph

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PREFACE

This book uniquely summarizes approaches for developing dermatological drugs in a regulated environment from the perspective of the pharmaceutical industry. Drugs may be new chemical entities or known compounds that have been repurposed and potentially reformulated for dermatological indications. The development of systemic drugs shares many common features across indications; however, the development of topical drugs for skin diseases (topical dermatological drugs) has many unique requirements that will be highlighted in this book.

While there are many manuscripts and review articles that summarize the outcomes of clinical trials, not many studies are reported when they have failed to meet desired endpoints or are considered lacking attractiveness from the prescribers' community or from the manufacturers. Nonclinical toxicology studies are rarely reported to medical or scientific communities. The industry is aware that the design and outcome of late-stage clinical studies such as phase 2, 3 and 4 studies should be disclosed in a timely manner, but there is no regulation or consistency in reporting results. Pharma is leading the effort, and some pharmaceutical companies have created their own disclosure policy to report results in their websites and have been following the policy, however the websites are not so well known or provide easy to use search functions for external users.

Clinical development for dermatology, including clinical pharmacology considerations, often differs from standard development for other indications and routes of administration, especially in topical drug development because patients with skin conditions may tolerate and/or absorb the drug differently than otherwise healthy individuals. Recent acquisitions of dermatology-specific corporations by large pharmaceutical companies sometimes face challenges in topical dermatological drug development when the large corporations do not have the relevant experience and skill sets, and underestimate the investment needed for development.

To date, there is no textbook addressing dermatological drug development to explain and illustrate why unique nonclinical and clinical studies are necessary and how they are typically designed and conducted.

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However, we can think of many reasons why such a book does not exist. Nonclinical and clinical studies related to drug development are often conducted by pharmaceutical companies. These studies are closely tied with regulatory submission to obtain marketing approval of the drug. The design and execution of such studies are confidential as they are core to each company's corporate strategy. When the new drug application is submitted to the regulatory authorities, the team is often dissolved, and core members will move on to other projects, often in completely different therapeutic areas. Drug developers often rely on their experience and updated regulatory guidelines in the design of drug development or in specific therapeutic areas. The drug development process is also an evolving process that is characterized by communicating, negotiating, and agreeing with regulatory agencies, such as the FDA, EMA and PMDA.

The authors of this book are fortunate to have years of experience in dermatological drug development and have developed oral, topical, and biological treatments for multiple skin diseases. While there is no complete guidance of the drug development process for each indication, there are always useful learnings that can apply to the future. The intention of this book is to share the knowledge, experience, and learnings that these authors have accumulated in the course of their experience to facilitate future dermatological drug development.

The authors acknowledge that there are several important therapeutic areas that are not discussed within the context of the following chapters. Oncology dermal drug development is a challenging therapeutic area with a significantly different path of clinical development, especially for skin cancers including melanoma. Owing to its complexity, the authors did not cover this topic in this book and chose instead to focus on more common dermal disease indications.

The target audience for this textbook is multifaceted: experienced drug developers entering the dermatology field, project leaders in biotech or pharmaceutical companies that are responsible for leading dermatological drug development, academic researchers that want their dermatological drug seeds to be attractive when transferring to the industry, or curious scientists that want to understand dermatological drug development. The authors are excited that many novel drugs are in the development pipeline in the industry in general. Many new drugs for patients and options for physicians to treat different dermatological diseases will be introduced in the coming decades. This book is intended to give a flavor of practical

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dermatological drug development and support future clinical innovation in dermatology.

It is a great time to be in dermatology!

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CHAPTER 1

OVERALL DRUG DEVELOPMENT PROCESS FOR SKIN DISEASES

Overview

The development pathway of topical products for the treatment of dermatologic conditions differs from the more traditional injection, tablet or capsule development for systemic targets. For example, many clinical pharmacology (or phase 1) studies, such as irritation, sensitization and even maximum usage pharmacokinetic studies are often delayed until the final formulation, strength, and dosing regimen have been established in safety and efficacy (phase 2) trials. For systemic drugs, the first human study is often conducted on healthy volunteers to establish the safety, tolerability, pharmacokinetics and pharmacodynamics. However, for topically applied drugs for dermatological conditions, the skin barrier may be compromised—studies conducted in patients with healthy skin may therefore be irrelevant or misleading. A topical product is designed to be effective at a localized site, and the active compound(s) must penetrate to the site of action (e.g. dermis or epidermis) and result in minimal skin irritation. Ideally, low systemic exposure is desired. Overall, dermatology targets can be complex, and topical delivery can be complicated as changes to a formulation during development of a product may require many studies to be repeated, increasing the cost and time of development. Topical products differ from transdermal products, as the goal with the latter is to achieve systemic exposure, where the target exposure is more often better defined.

For the development of any new potential drug product, it is important to develop a target product profile to address the ideal delivery profile, site of action, dosing regimen, and clinical claims. This method of starting with the end in mind will help to keep the development of the product focused on the ultimate goal: a product that meets regulatory requirements and commercial expectations. A complete target product profile will include information from all disciplines and will consider the evidence for each

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labeling statement. The FDA has issued a draft Guidance for Industry outlining their thinking on this topic.[1]

Currently there is no single guidance document delineating specific steps for the development of dermatological drug candidates. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) was formed to achieve greater harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner. The ICH guidelines are divided into the four categories: quality, safety, efficacy, and multidisciplinary.[2] These guidelines are updated through discussions between agencies and the industry. Health authority agencies regulating the development of topical products involved in the ICH process include the Food and Drug Administration (FDA) in the United States (US), the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA), and the Pharmaceuticals Medical Devices Agency (PMDA) of the Ministry of Health, Labor, and Welfare in Japan. In the US, dermatological products are regulated by the Division of Dermatology and Dental Products in the Office of New Drugs in the Center for Drug Evaluation and Research (CDER). These agencies develop guidelines and guidance, and some disease specific and route-specific guidelines also exist. For nonclinical evaluations, regulatory guidelines that specifically refer to dermal administration have been published by the US Environmental Protection Agency (EPA) and the Organization for Economic Cooperation and Development (OECD) for safety evaluation of chemicals. These guidelines focus on *in vitro* studies or on safety evaluation in rodents. The most relevant guidance represents a consensus across the regions of the European Union (EU), Japan, and the US regarding the type and duration of nonclinical safety studies and their timing, and supporting the conduct of human clinical trials and marketing authorization for pharmaceuticals is the ICH M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing

[1] Food and Drug Administration. *Target Product Profile—A Strategic Development Process Tool*. Guidance for Industry. March 2007. https://www.fda.gov/media/72566/download.

[2] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). "Official Website." Accessed October 2019. https://www.ich.org/products/ctd.html.

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Authorization for Pharmaceuticals.[3] Informal guidance on dermal product drug development has been presented at scientific meetings such as the Society of Toxicology or in non-governmental publications.

The studies and data package required for selection of a new dermatological product varies depending on whether the compound is a new chemical entity or is repurposed from an already established formulation and/or route of administration.

Dermatological drug substances often vary in the starting point for development and each project may have a different quantity and quality of existing data that may be used to satisfy some of the nonclinical safety data requirements to support a new clinical development program for dermal administration. The studies and data package required for a new chemical entity with little or no previous nonclinical safety data will be considerably different than for a compound being repurposed from an already approved or established formulation and/or route of administration, which will have a significant amount of existing data. Repurposed compounds could include the addition of a dermal route of administration during development, previously approved via a different route, and/or previous development discontinued for various reasons, reformulated drug substances previously approved in a topical dermatological product, or inclusion in a new fixed-dose combination product.

Another important decision at the beginning of the drug development process is to confirm the relevant regulatory approval pathway(s). For example, in the US, a new chemical entity would follow a 505(b)(1) pathway with submission of a full NDA with supporting data to the regulatory agency. For generic equivalents (same dose, route), an abbreviated NDA (ANDA) or 505(j) would be submitted, establishing bioequivalence. It may also be possible to use a bridging approach (505(b)(2))[4] for active pharmaceutical ingredients that have been previously approved, for which modifications are being made (such as more convenient dosing regimen, a different route of administration, or a different indication). This regulatory

[3] Food and Drug Administration. *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*. Guidance for Industry. January 2010. https://www.fda.gov/media/71542/download.
[4] Food and Drug Administration. *Applications Covered by Section 505(b)(2)*. Guidance for Industry (Draft). October 1999. https://www.fda.gov/media/72419/download.

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Figure 1-1: Early Stage Discovery Overview

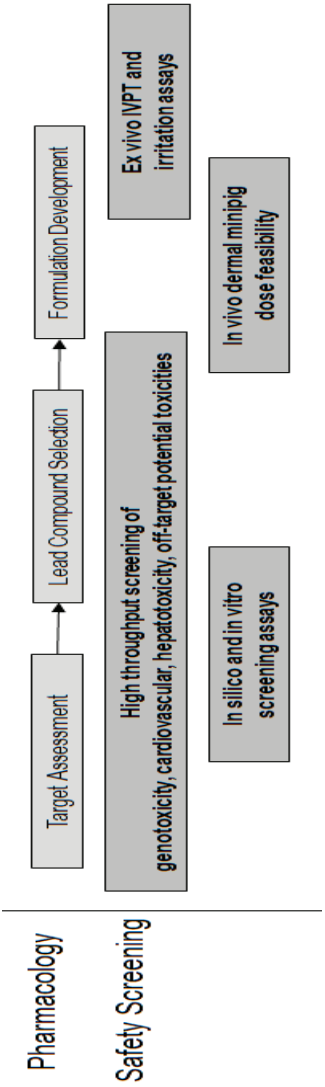

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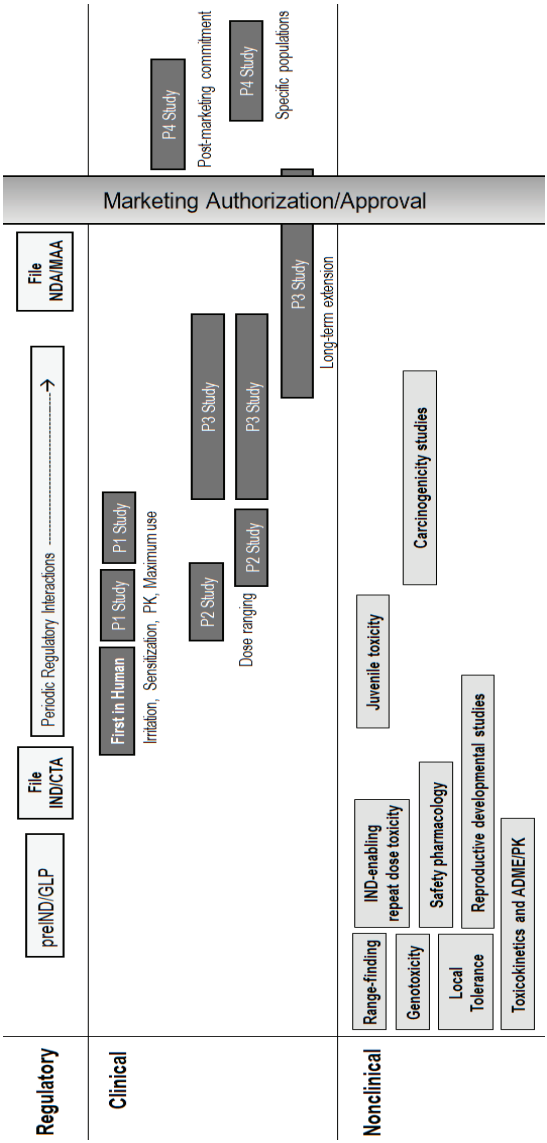
Figure 1-2: Dermatological Drug Development Overview



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pathway specifically relies on the established nonclinical safety and clinical safety and/or efficacy of the active pharmaceutical ingredient in the approved product (the reference listed drug (RLD)); the nonclinical and clinical studies therefore needed to support an initial investigational new drug (IND) application and subsequent NDA approval, respectively, for the new product are typically less extensive. The label wording to be bridged, along with the regulatory pathway, should be established early in development and is generally a topic for discussion at the pre-IND meeting. In Europe, there is a hybrid application that is somewhat analogous to the FDA's 505(b)(2): the legal basis is based on Article 10 of Directive 2001/83/EC which covers a generic, hybrid or similar biological application.[5,6,7]

[5] Camargo. "Does Europe Have a Pathway for Approval of Drugs Analogous to the FDA's 505(b)2 Pathway?" (2009) Accessed December 14, 2019. https://camargopharma.com/resources/blog/does-europe-have-a-pathway-for-approval-of-drugs-analogous-to-the-fdas-505b2-pathway.

[6] European Parliament and of the Council on the Community code relating to medicinal products for human use. Directive 2001/83/EC, as amended by 2002/98/EC, 2004/24/EC, and 2004/27/EC. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/directive-2001/83/ec-european-parliament-council-6-november-2001-community-code-relating-medicinal-products-human-use_en.pdf.

[7] European Medicines Agency. *European Medicines Agency procedural advice for users of the centralised procedure for generic/hybrid applications*. EMEA/CHMP/225411/2006. August 2019. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-procedural-advice-users-centralised-procedure-generic/hybrid-applications_en.pdf.

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Table 1-1: Development Regulatory Pathways

Development Regulatory Pathways		US FDA	EMA
New chemical entity	A new drug that has not been approved for any indication	Traditional New Drug Application (NDA) process: 505(b)(1)	MAA (Marketing Authorization Application)
Repurposed	A new formulation, new route of administration, or new indication for a drug that has been previously approved	505(b)(2)	Generic/hybrid MAA
Generic	A drug that is qualitatively and quantitatively the same (Q1/Q2/Q3) as the reference listed drug	Abbreviated NDA 505(j)	Generic/hybrid MAA

A number of FDA workshops that included representatives from academia and industry have been held over the past decades to progress the principles and criteria in the development and optimization of topical therapeutic products. In 1990,[8] the major objectives were:

(1) To review and evaluate available information on topical drug products;

(2) To evaluate relationships between pharmacological activity, drug delivery, and clinical efficacy;

[8] Shah, V. P., C. R. Behl, G. L. Flynn, W. I. Higuchi, and H. Schaefer. "Principles and Criteria in the Development and Optimization of Topical Therapeutic Products." *Journal of Pharmaceutical Sciences* 81, no. 10 (October 1992): 1051–54. https://doi.org/10.1002/jps.2600811020.

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(3) To identify ways to optimize topical drug delivery to target sites;

(4) To identify important principles in the development and optimization of topical drug products;

(5) To raise possible concerns related to the local and systemic toxicity arising from topical drug delivery; and

(6) To discuss regulatory concerns in the evaluation of topical drug product.

At that time, guidance suggested conducting studies with clinical endpoints because there were no guidelines for the use of laboratory models (e.g. *in vitro*, animal or mathematical) to predict and optimize the clinical efficacy of topical drug products. It was hoped that there could be a greater understanding of how to optimize topical products without the need for large, lengthy, and expensive clinical studies, and that there could be more reliance on other scientific tools. The complexity of targeting skin exposure was recognized along with the limitations of flux and/or drug retention in the skin for dermatological products. The importance of developing prototype formulations in early development studies was recognized, as well as pursuing all reasonable means to optimize skin uptake/retention before evaluating the clinical activity of the drug.

Generic drug development is important in providing alternatives to branded products. For topicals, this may require reverse-engineering to match the reference listed drug (RLD) to ensure qualitative (Q1) and quantitative (Q2) formulation similarity and similarity in formulation microstructure (Q3). If feasible, the formulation goal for a generic topical drug product is qualitative and quantitative sameness (Q1 and Q2, respectively) as the RLD. The ability to use *in vitro* skin permeation (IVPT) studies as a tool to support formulation differences between the test generic product and the RLD to ensure a successful pivotal clinical study has been the topic of recent discussion.

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Nonclinical Development

It is important to address the following issues before conducting clinical studies:

(1) Are the physicochemical properties of the drug well understood?

(2) Has the pharmacologic activity of the drug been demonstrated or adequately predicted?

(3) Are pharmacological models used to assess/predict the drug's activity relevant and well conducted?

(4) Were relevant research vehicles used in screening for activity?

(5) Is the target tissue (epidermis, dermis, or some specific cellular group within these strata) known?

(6) Has drug delivery and drug uptake/retention within skin layers been adequately evaluated?

(7) Does the drug penetrate the skin?

(8) Is the formulation stable through needed shelf-life?

(9) Is the drug metabolized by the skin?

(10) Does the drug stay dissolved at the right concentrations?

Additional parameters of consideration include: 1) time-dependence for drug delivery and retention and optimal dosing regimen; 2) cleansing schedule of the skin surface and effect on delivery and retention; 3) analytical sensitivity limitation and requirements; and 4) factors such as pH, temperature, hydration, occlusion, anatomical site and their influence on delivery. The nonclinical safety assessment of drug products generally includes safety pharmacology studies, general toxicity studies, toxicokinetic and nonclinical pharmacokinetic studies, reproductive toxicity studies, genotoxicity studies, and for longer duration of use, an assessment of carcinogenic potential. Other nonclinical studies to assess immunotoxicity (if necessary due to potential for immunomodulation), juvenile animal toxicity (for pediatric indications), and local tolerance (e.g. phototoxicity, ocular irritation, dermal irritation) are also conducted.

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The main objective in the nonclinical development of dermatological drug products is to identify any potential toxicity and describe the pharmacokinetic profile (toxicokinetics) after administration by the dermal route. In addition to being a barrier to drug absorption, the skin is in general metabolically active, with lower than the liver capacity but different enzyme composition. Potential metabolism in the skin is therefore taken into consideration when evaluating local efficacy and safety. The clinical indication, duration of treatment, and conditions under which a topical dermatological drug product will be applied, are all important aspects to be taken into account in the nonclinical development plan. Nonclinical studies evaluate the systemic target organs of toxicity, describe drug skin exposure and systemic plasma exposure, assess skin and plasma metabolism/distribution/excretion, as well as determine potential effects on pharmacology and efficacy. Additionally, nonclinical studies are conducted to define safety margins for the dermal and systemic toxicity studies, local tolerance studies, and other special toxicity assessments in order to support the clinical trials and ensure safety for the patient. This helps inform safe starting doses for the clinical trials and defines parameters for the monitoring of potential adverse effects. Systemic exposure profiles (concentration versus time) via dermal administration can vary significantly from other routes of exposure (e.g. lower Cmax, higher AUC) and may impact the safety and efficacy profile of a drug substance compared with an alternative route of administration.

Impact of Formulation

Formulation development is one of the major areas covered by chemistry, manufacturing and control (CMC) functions in the pharmaceutical industry. The detailed discussion is beyond the scope of this book, but can be found in a recent comprehensive publication by experts in the discipline.[9]

The FDA Guidance, Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route, provides a guideline that may streamline development of a dermal product in which the active ingredient was previously developed for an alternate route or formulation. Excipients in the formulation, especially penetration enhancers (for example, propylene glycol), may influence the

[9] Brown, Marc B., and Adrian C. Williams. "The Art and Science of Dermal Formulation Development," Boca Raton: CRC Press. January 2019. https://doi.org/10.1201/9780429059872.

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bioavailability of the active pharmaceutical ingredient as they are used to improve transdermal drug delivery by reversibly decreasing the barrier resistance of the skin.

Additional systemic toxicity studies might be recommended if the available toxicity information is not sufficient to support the exposure measured with the new formulation or if a significantly different pattern of exposure results from the new formulation. An adequate evaluation of the pharmacokinetics and absorption, distribution, metabolism, and elimination (ADME) of the drug substance is recommended for new formulations. When comparing the pharmacokinetics/ADME of a new formulation with a previously-approved formulation, it is important to examine the shape of the concentration-time curve and not just the total area under the curve. For example, alterations in absorption or the dosing frequency can produce significantly different concentration-time profiles that might lead to different toxicological effects.

Generally, no further studies for the evaluation of systemic toxicity will be required in circumstances where: a) absorption of the product can be demonstrated to be so low that the possibility of systemic effects can effectively be ruled out, and/or b) the product is absorbed but systemic toxicity has previously been adequately investigated (Note for Guidance on Non-Clinical Local Tolerance Testing of Medicinal Products).[10] Given that a new drug product can be reformulated from an existing drug product (e.g. change of excipients) or a new indication (e.g. from oral to intradermal to topical) in which a new formulation will be needed, there is a comprehensive data set available from approved reformulations that enables existing pharmacokinetic and safety data to be used for support of the clinical studies. In addition to pharmacokinetic and local tolerance studies, a single pivotal toxicity study in non-rodents to cover the duration of intended clinical use may be sufficient to evaluate any novel pharmaceutical excipients in the newly formulated drug product.

Excipients considered for use in dermal products can be searched using the FDA Inactive Ingredient Database[11] for the intended route of

[10] European Medicines Agency. Guideline on non-clinical local tolerance testing of medicinal products. CHMP/SWP/2145/2000. October 2015. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-non-clinical-local-tolerance-testing-medicinal-products_en.pdf.

[11] Food and Drug Administration. "Inactive Ingredient Search for Approved Drug Products." Accessed December 14, 2019. https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.

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administration and at concentrations less than or equal to those listed in an FDA-approved drug product. For any excipients in the drug product that have not been previously used in an FDA-approved drug, the FDA Guidance on Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients should be followed to qualify the excipient(s). A novel excipient will likely require a full safety (toxicology) assessment.

Clinical Pharmacology

A clinical pharmacology development plan is important to support the future product label. There are required sections to address the pharmacokinetics/ADME, dosing recommendations, food effect (for oral formulations), specific populations (e.g. hepatic/renal impairment, elderly, pediatrics, sex, racial or ethnic groups, pregnant or lactating women), drug-drug interactions, and pharmacogenomics.

Ideally, consult a clinical pharmacologist early in development as a clinical pharmacology development plan can support activities in the nonclinical space through product approval. Clinical pharmacologists have the tools to enable a dose rationale including safety margins and projections for systemic exposure. If the target exposure in the skin, at the site of action, is known, and IVPT studies have been conducted, the optimal formulation and concentration strength may be addressed prior to clinical studies. It is important to understand the site of action: if in the skin, where in the skin? Is it the epidermis or dermis, or is it important that the drug be picked up by the lymph and/or systemic circulation?

A typical clinical pharmacology development plan will differ by route and indication, what is known about the disease, target, and compound class. For topically-applied products, local safety should be addressed in early studies as irritation/sensitization is often formulation-dependent. One difference from traditional clinical development of new drug products is that the first in human study may be conducted in the intended patient population because the skin barrier is affected for many dermatological conditions; studies in volunteers with healthy, intact skin, may therefore not be relevant for either local evaluation or for lack of quantifiable systemic absorption through an intact skin barrier. Ideally, pharmacokinetic sampling should be included in early clinical studies to determine the bioanalytical sensitivity that will be required to adequately characterize the pharmacokinetic profile and to optimize sampling times in definitive studies (such as the maximal usage trial (MUsT)).

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An early clinical plan should include evaluation of the mechanism of action, biomarkers, including gene suppression, and pharmacodynamic endpoints as evidence of target engagement. A well-defined biomarker strategy can enable a solid dose rationale, evaluation of proof of concept, and minimize wasted time and money spent on an unsuccessful clinical study.

For topically-applied products, dedicated irritation, sensitization, phototoxicity, photoallergenicity, and MUsT studies are generally required. These studies may be conducted at any time during development; however, they should be conducted with the to-be-marketed formulation and formulation strength/concentration.

The relevance of products that might be applied concurrently is not often considered; however the potential for drug-drug interactions or for products to influence the absorption of each other may have an impact on safety and/or efficacy. If the drug is a prodrug, intended to be converted within the skin to a pharmacologically active drug, then evaluate the potential for the applied drug (prodrug), to be rapidly converted to the active moiety, and whether relevant metabolizing enzymes are present in the skin. For a systemically present drug, determine whether there are metabolites that need to be characterized.

All new drug products are required to assess the potential for QTc prolongation and Torsades de Pointes. Digital ECG and QTc monitoring can be part of initial clinical trials, and time-matched concentration-QTc (cQTc) slope analyses can be conducted if there is sufficient systemic exposure and potential maximum usage (applied to maximal body surface area (BSA) likely to be treated in patients with upper end of severity for the condition) is covered. It is important to understand whether your drug has an effect on heart rate (such as anticholinergics used for hyperhidrosis). A thorough QT study may be necessary if the drug does have an effect on heart rate or if supratherapeutic systemic concentrations have not been achieved.

It is also important to consider the relevance of specific populations (e.g. elderly, renal/hepatic impairment, pediatrics). The need to conduct dedicated studies will depend on systemic absorption and route of metabolism/route of elimination. It is important to understand what happens to the drug that does get absorbed, and conducting metabolite identification in human plasma is recommended. For topical dermatological products, there may be population differences in the skin barrier that are relevant in neonatal and elderly skin. If development is planned in Japan, separate bridging studies

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for systemic exposure, irritation, and/or sensitization, with the design prospectively agreed with the Pharmaceuticals and Medical Devices Agency (PMDA), may be required before inclusion of Japanese patients in larger clinical trials.

Late-Phase Clinical Development

Late-phase or late-stage drug development usually refers to phase 2, phase 3, and phase 4 clinical studies and may also include long-term, open-label studies for chronic conditions. The standard process of late-stage clinical drug development is similar, regardless of the route of administration route (oral, subcutaneous or intravenous injection, or topical/cutaneous). The overall likelihood of approval from phase 1 for all developmental candidates was 9.6%,[12] and the cost of the development becomes higher as the development stage advances. It is rightly said that killing a project at early stage of drug development is also a success as development costs can be used in other areas. It is highly desirable to predefine Go/No Go decision criteria when discussing the target product profile. It is always difficult to make a decision when the study result is not robust enough and the business environment involves many stakeholders. The target product profile should therefore be considered as the benchmark and adjusted with the changing environment of the competitive market.

Phase 2 Studies

Phase 2 studies are initiated after the drug has been shown to be safe across a range of doses in phase 1 studies, which typically enroll 20 to 100 healthy volunteers or people with the disease/condition of interest. Phase 2 studies may also be called dose exploration studies, dose ranging studies, dose response studies, or dose confirmatory studies. For topical dermatological drug development, a phase 1 study may not always be required; the first study may be in patients and considered to be phase 2 with or without dose ranging. The ultimate goal of phase 2 studies is to identify the dose(s), dosing regimen, and treatment duration to evaluate in the pivotal phase 3 studies, as well as the number of patients needed to

[12] Thomas, David W., Justin Burns, John Audette, et al. "Clinical Development Success Rates 2006-2015." *Biotechnology Innovation Organization Industry Analysis* (2016): 1–28. https://www.bio.org/sites/default/files/legacy/bioorg/docs/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf.

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demonstrate a significant treatment difference in pivotal studies. Considering the high cost of phase 3 studies, it would be ideal to identify a single dose and dosing regimen to move forward. To achieve this goal, several phase 2 studies may need to be conducted.

There are many objectives in phase 2 studies. It is important to demonstrate whether the drug is active in the human target tissue—target engagement (if it was not shown in the phase 1 studies). In the phase 2 setting, it would be informative to see pharmacodynamics or changes in biomarkers, assuming appropriate effects have been identified that are predictive of the desired clinical response. For skin diseases, skin biopsies can be useful to demonstrate biomarker changes. Biomarkers may include a certain DNA, RNA, protein, or blood chemistry that have a known response when the disease condition changes. For example, when developing a drug to treat psoriasis, it would be desired to show that IL-17 in the skin will be downregulated after administration of the drug. In the study, it is also desirable to see how soon the downregulation happens and which dose is the most effective and safe to downregulate the biomarker. Ideally, signals in the biomarkers appear sooner than the clinical effect. The early phase 2 studies (phase 2a) can be conducted in a relatively small population and over a shorter duration, allowing for early determination of the potential for efficacy while minimizing resources and cost. For example, if IL-4 and/or IL-13 downregulation is observed within 2 weeks in 20 patients with atopic dermatitis treated with the drug (but not observed in patients receiving placebo), even if there is not much clinical improvement, the dose-ranging phase 2 studies may be designed with confidence. In the early stage of phase 2 studies, it is expected to demonstrate proof of mechanism (POM) and proof of concept (POC). If there are no surrogate endpoints, such as biomarkers that precede clinical signals, POM and/or POC may need to wait until later phase 2 studies (phase 2b) and evaluation of clinical endpoints. Lacking surrogate endpoints that reliably predict clinical outcome is viewed as a development risk. On the other hand, POM and/or POC that can be demonstrated during phase 1 or 2a is an advantage for drug development. Collaboration with non-clinical pharmacology studies, clinical pharmacology, and translational science/medicine has tremendous benefits. However, established biomarkers are not always available due to lack of animal disease models and biological differences between humans and animals.

Demonstration of dose response is an important goal of phase 2 studies. Usually 3 to 7 arms are included in a study to evaluate different doses (strength/concentration) and dosing regimens (application frequencies). For

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topical products, the total applied dose will also vary with the BSA of application.

Ideally, placebo has no efficacy, but a placebo effect or placebo response is very common in skin diseases. It is especially true for topical therapies. There is no true placebo for topical therapies because the drug product vehicle is used as a control, and it often has an emollient effect. One study may include only twice daily dosing, with a second study including only once daily dosing. Alternatively, you can include both once- and twice-daily dosing in the same study. In this case, there should be two separate placebo (or vehicle) arms in the study design as it is impossible to mask the dosing frequency. If an emollient effect from the vehicle can be disregarded for the target skin disease, all participants should apply the study drug twice a day, but one of the applications must be a placebo (or vehicle) for once-a-day dosing of the active treatment group to mask the dosing frequency.

If a minimally efficacious (or non-efficacious) dose, maximally efficacious dose, and the dose in-between could be identified, it would be a great achievement. If the maximally efficacious dose has a similar safety profile with the in-between dose, the maximally efficacious dose can be further explored. The maximally efficacious dose may be safe for adults but may not be safe for pediatric patients. So, the execution of phase 2 studies may be more practical if divided into two or more studies depending on factors such as age, dosing frequency, and endpoints. Of course, cost efficiency is one of the important factors, but first, it is critical to be clear as to the overall objectives of the study. To see clinical changes in a study to treat alopecia areata and demonstrate dose response, 4 weeks' duration is not sufficient, and 12 to 16 weeks of treatment may be necessary. It is noteworthy that regulatory agencies are very keen on dose response and dose selection. It is naturally understandable, since nobody wants to expose patients to unnecessarily high doses or ineffective low doses. The benefit of using the drug must exceed the risk of the drug for the further development. When completing the phase 2 studies, it is important to define the risk-benefit as well as to develop a dose justification document or statement. Such a justification may be very straightforward or very complicated, depending on the drug's safety and efficacy profile in the target population.

Some regulatory authorities may request development of a lower dose than other authorities because their view on risk/benefit assessment is different. In the above example, if the maximally efficacious dose has a similar safety profile to the in-between dose, the maximally efficacious dose can be further explored. On the flip side, if the in-between dose has

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acceptable efficacy and only a slightly better safety profile, the agency may require evaluations of this in-between dose. This type of discordance creates complexity when designing a global drug development program.

Drug development is often conducted in adults first, to establish safety and efficacy before dosing in a pediatric population. However, pediatric populations are now recognized as an underserved area in terms of drug development and market access; pediatric patients therefore need to be included in studies at an earlier stage of drug development. In addition, many dermatological indications are for pediatric populations; a pediatric study plan is therefore an important component of the overall development plan. The pediatric plan will describe the planned studies for each pediatric age subset and, if applicable, will include a rationale for why a waiver and/or deferral is being requested for some or all pediatric age subsets.[13,14] For the EMA, a pediatric investigation plan (PIP) is also required and is generally submitted after phase 1 pharmacokinetic studies have been completed. For the FDA, an initial pediatric study plan (iPSP) should be submitted after phase 2 studies for any drug that includes a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, unless the drug has been granted orphan designation for the proposed indication.

For clinical trials for atopic dermatitis, there is a trend to include adolescents and adults in the same study. If the dose response is similar between adults (≥18 years) and adolescents (12 to <18 years) then the same dose may be used. For children (2 to <12 years) and infants (0 to <2 years) consider whether a dose response study in the patient population is necessary. Depending on the product experience, there may be a justification for not conducting the study and including them with adults in a phase 3 study. Consider the operationally and scientifically supported rationale for the necessity to test the in-between dose in the phase 3 study, in addition to evaluating a maximum dose. There are many options to think about and the budget is often a constraint. Creativity is required to overcome these challenges. If introduction of the drug is intended globally, it is a

[13] Food and Drug Administration. *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans*. Guidance for Industry (Draft). March 2016.
https://www.fda.gov/media/86340/download.
[14] European Medicines Agency. "Paediatric Investigation Plans."
https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans.

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reasonable choice to use a pediatric age definition of less than 18 to align with definitions from the EU regulatory system. Historic examples and stories are available about discordance of medical science and regulatory processes about the challenges of pediatric drug development.[15]

At the end of phase 2, safety and efficacy data are viewed as limited, even if the dose response is clearly demonstrated. These data are used to refine research questions, develop research methods, and design new phase 3 protocols. Introduction of new endpoints to the phase 3 studies is not preferred. It is best to test all the endpoints in the phase 2 studies to provide information about treatment effect and variability that is important for adequately powering the pivotal phase 3 studies. If there is an intention to include patient reported outcomes (PRO) data in the product label, these endpoints should also be included in the phase 2 studies. If that is not possible, separate studies may be necessary. Development of a disease-specific PRO requires validation. Discussions with the regulatory authorities may help to identify such needs, and the FDA encourages discussion at an early stage of drug development.[16]

If dose response studies were completed in different indications, some of the steps of dose finding in the target indication may be simplified or skipped completely. However, it is a standard approach to include dose justification rationale for the target study population in the briefing document for the end of phase 2 (EOP2) meeting prior to proceeding to the phase 3 studies.

Lessons learned from similar studies for the same or similar indications are very informative and critical to designing a study. In the immune inflammatory skin disease arena, there are many common study design features between psoriasis and atopic dermatitis. It is always more challenging when designing the first study in a new therapeutic area, so called “first in class”. It is important to obtain sufficient advice from experienced drug developers from similar therapeutic areas in addition to the regulatory authorities.

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[15] Rose, Klaus. “The Challenges of Pediatric Drug Development.” *Current Therapeutic Research, Clinical and Experimental* 90 (2019): 128–34. https://doi.org/10.1016/j.curtheres.2019.01.007.

[16] Food and Drug Administration. *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. Guidance for Industry. December 2009. https://www.fda.gov/media/77832/download.

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Safety is paramount, and assessment of all adverse events is performed during clinical trials. To understand the safety profile of the drug, it is important to prepare a cumulative safety assessment plan. It is also a requirement to submit the Development Safety Update Report (DSUR) to the regulatory authorities every year after starting clinical trials. In the report, it is required to assess the drug safety across the indications not only with the certain drug product, but with the same or similar active pharmaceutical ingredients. These assessments and document preparations become labor intensive once entering the phase 2 stage, so it is important to prepare resources and have project management, or at least time management, for the process. If the process is not established internally, it is worthwhile considering using a contract research organization (CRO) that has the relevant expertise.

Phase 3 Studies

The FDA has a standard requirement for 2 confirmatory phase 3 studies that demonstrate consistent results. The studies do not have to be identical, but critical aspects should be replicated. This is particularly important when conducting global clinical trials to satisfy requirements from multiple regions. For example, if the EMA requested a 1-year study period, but FDA's requirement was only 12 weeks, it is possible to plan for one 1-year study and one 12-week study, as long as the critical aspects are replicated in both studies. If the EMA requested adding an active comparator drug, it is a reasonable option to include the active comparator in the 1-year study but not in the 12-week study. Although the FDA usually does not request an active comparator arm, there may be a benefit to having comparative data within a study considering recent payer environment in the US. If there is an intention to include the active comparator results in the label, it is critical to discuss with the FDA at the end of phase 2 (EOP2) meeting. A successful phase 3 program needs to demonstrate statistically significant superiority or at least non-inferiority over the active comparator. How to predetermine statistical significance and non-inferiority margins are always tough negotiations, which require many references and sometimes conducting a separate epidemiological study. These rationales and supportive arguments should be included in the EOP2 background document in order to have a successful meeting. It is important to keep in mind that only one hour is allocated to an EOP2 meeting, while many items are to be discussed. It is also important to prepare an internal rationale since having an active comparator arm in the phase 3 study increases costs, which may not be justified. If the sponsor is not interested in having the comparative data on

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the label, it may not be necessary to demonstrate statistical significance. Alternatively, the results can be published in a peer journal, and negotiation with payers about reimbursement becomes available. However, these approaches should be well prepared in order to publish in a timely manner.

Under certain circumstances, the FDA may agree that a single phase 3 study is sufficient for approval. If a phase 2 study demonstrated unequivocal results or if the indication is for a rare disease (and the drug has obtained an orphan drug designation), it is worth negotiating with the FDA at the EOP2 meeting, or ideally prior to it.

At the EOP2 meeting, it is important to clarify with regulatory agencies about what a successful phase 3 study looks like, particularly obtaining agreement about the primary endpoint(s). It is best to have the same primary endpoint across the regions. However, there have been historical differences between the FDA and other agencies in their preferences. The FDA has been clear that the primary efficacy endpoint should be clinically meaningful and reflect clinical practice, but the assessment needs to be performed without referring to the condition of the previous visits. Regular dermatology practice uses mostly visual and subjective assessment, and the physicians make comparisons with previous conditions. If the assessment makes references to previous conditions it is called dynamic assessment, and if not, it is called static assessment. Subjective assessment is called global assessment in clinical studies. For many dermatological clinical trials to satisfy FDA requirements, the sponsors need to use static (i.e. without reference to previous conditions) and global (i.e. relatively controlled subjective) assessments. These are called either investigator global assessment (IGA) or physician global assessment (PGA). Please refer to disease specific development sections about the details.

For topical dermatological development, local skin reactions, including irritant contact dermatitis and allergic contact dermatitis, are obvious interests or concerns and need to be assessed at an early stage of development. The FDA's view on dermal safety is evolving, and the sponsor should discuss when and how to assess local skin reactions. Recently, it seems that assessment of dermal safety within phase 2 and phase 3 studies with the target study population is becoming more favorable from

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the FDA's perspective, even with the operational challenges acknowledged.[17]

Conducting phase 3 studies is a huge endeavor and commitment. It is very costly and requires a great deal of resources. As it is necessary to show statistical significance of the investigational drug product over a comparator, the sample size of some studies may reach 5000 patients. Even if it is possible to demonstrate statistical significance in a small study with 100 patients, it is still necessary to satisfy a minimum number of patients for safety population that is required for registration. In order to design a successful phase 3 study, analyzing phase 2 results from various aspects is critical. This includes not only regular statistical analysis of phase 2 outcomes, but also assessment of the study operations, such as distribution of the study centre locations, investigator types and experiences, and the number of patients at each site. These factors may change between phase 2 and phase 3 studies, and any potential change should be fully assessed. There are a lot of risks in drug development, but developing strategies to minimize and mitigate the risks and implement these strategies throughout development, particularly phase 3, has a huge impact on whether or not a successful study is delivered. This process needs experience. For that purpose, the pharmaceutical or biotechnology company needs to hire highly skilled individuals who have a proven record of successful phase 3 studies.[18] Well planned and managed operations of the studies, and the design of the study itself, are equally important for a successful outcome. Tight control of study execution can minimize the standard deviations of the efficacy endpoints, and experience can tell where to control. It is an industry standard to outsource study operations to contract research organizations (CROs), but selection of the CROs is not an easy task. Some companies may not have the freedom to choose the CROs, but streamlined communications, proper sponsor oversight, and collaboration with the CRO are keys to a successful execution of the phase 3 studies.

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[17] Food and Drug Administration. *Human Dermal (Skin) Safety Testing for Topical Drug Products: Regulatory Utility and Evaluation; Public Workshop; Request for Comments*. Silver Spring, Maryland; September 2018. https://www.fda.gov/drugs/news-events-human-drugs/human-dermal-skin-safety-testing-topical-drug-products-regulatory-utility-and-evaluation-public.

[18] Friedhoff, Lawrence T. New Drugs. An Insider's Guide to the FDA's New Drug Approval Process for Scientists, Investors and Patients. ISBN13: 978-1419699610. Reprint, PSPG Publishing, 2009.

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The value of project management cannot be underestimated in drug development. There are many activities being conducted in parallel across all disciplines, including clinical, safety, clinical pharmacology, toxicology, regulatory affairs, and chemistry, manufacturing, and control (CMC). Successful completion of phase 3 studies is not the final goal. Drug approval is a mission. Patients are waiting.

New Drug Application (NDA) / Marketing Authorization Application (MAA)

While conducting the pivotal phase 3 studies, preparation of the documents for regulatory submissions seeking approval of the new drug product needs to be happening in parallel. Every single day counts. A 1-month delay in submission may cost several hundred thousand dollars. The application involves thousands of pages of documents in a format called the common technical document (CTD).[19] The majority of the modules are the same for an NDA (FDA), MAA (EMA), and J-NDA (Japan) to facilitate applications in multiple regions. The final application should tell the drug's whole story, from active and inactive ingredients, manufacturing process, packaging, nonclinical studies, and clinical studies through plans for post-marketing safety surveillance or registries. In addition to presenting analyses of data from the individual studies, it is also important to integrate key efficacy and safety data for pooled analyses. For example, the drug's effectiveness may be analyzed by combining data from two phase 3 studies, or by combining data from phase 3 with phase 2 studies. Integrated safety data is particularly important when discussing the drug's safety profile because the volume of safety data is still limited during the clinical development stage. Although the integrated efficacy discussion uses the same target disease population, the integrated safety discussion often includes different disease areas, as long as the active pharmaceutical ingredient is the same.

The regulatory agencies will review the application from multiple perspectives, including whether the drug is safe and effective in its proposed use(s); whether the benefits of the drug outweigh the risks; whether the drug's proposed labeling (package insert) contains the appropriate information; and whether the methods used in manufacturing the drug and

[19] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). "Official Website." Accessed October 2019. https://www.ich.org/products/ctd.html.

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the controls used to maintain the drug's quality are adequate for preserving the drug's identity, strength, quality, and purity.[20]

Table 1-2: New Drug Regulatory Review Periods

	FDA (US)	EMA (EU)	PMDA (Japan)
Standard review period	10 months plus 60 filing days	210 days	12 months
Accelerated review period (priority)	6 months plus 60 filing days	150 days	9 months
Required features for priority review	● Significantly improves safety or effectiveness ● Treatment for a serious disease	● Important in terms of public health and innovation ● Strong evidence ● Fulfills an unmet medical need	● No standard existing therapy or superior clinical usefulness as compared with the existing products in terms of quality of life of patients, efficacy, or safety ● Applicable to serious diseases or orphan drug designation

[20] Food and Drug Administration. *New Drug Application (NDA)*. June 2019. https://www.fda.gov/drugs/types-applications/new-drug-application-nda.

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It usually takes approximately 1 year for the FDA, EMA, and PMDA, unless it is designated to a priority review, to review the full NDA and make the decision whether or not to approve the drug product (Table 1-2).[21] During the review period, there may be several requests from the regulatory agencies for the company to provide additional information; these requests have a very short timeline for responding.

Phase 4 Studies (post-approval)

The main purpose of phase 4 studies is to expand the safety database and provide marketing support. Safety information is limited prior to the marketing authorization due to stringent enrollment criteria for phase 1 to phase 3 studies. After the drug has been approved and comes to market, it will be used by the wider public. For example, in the phase 3 studies, patients with a known ongoing malignancy are usually excluded because they could confound the data analyses; however, these patients still need treatment for their skin conditions and will use the product after approval. Another example is pregnancy. Prior to the marketing authorization, safety and efficacy data are often limited for pregnant women.

The format of phase 4 studies varies depending on the objective. A registry study may be used to collect pregnancy outcomes for women using the drug. A more traditional study design may be used to evaluate the efficacy and safety in a different target population. In competitive target disease areas, such as psoriasis, it is desirable to demonstrate superiority over a competitor's drug. These studies are not required for initial approval, but may be necessary to support the market. The drug label may be updated accordingly. Sometimes, additional studies are required by a regulatory agency as a condition of approval. These post-marketing commitment studies are discussed during the review period and may be initiated prior to, or after, the approval. If the product is transferred to another company (e.g. due to a merger of the companies or business development negotiations), the obligation for post-marketing commitment studies also transfers to the new company.

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[21] Nagai, Sumimasa. "Flexible and Expedited Regulatory Review Processes for Innovative Medicines and Regenerative Medical Products in the US, the EU, and Japan." *International Journal of Molecular Sciences* 20, no. 15 (August 3, 2019). https://doi.org/10.3390/ijms20153801.

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CHAPTER 2

SUPPORT FOR EARLY CLINICAL STUDIES

Nonclinical Discovery Development

Toxicity continues to account for more than 50% of compound attrition during the drug development process, and remains one of the major causes for a drug to be withdrawn from the market after approval. This concern contributes to the rising costs associated with clinical trials, leading to an unsustainable business model within the pharmaceutical industry. Improved early identification of toxicities associated with new drug substances and drug products allows for more efficient and effective drug development and enables resources to be focused only on those compounds most likely to succeed.[22]

Nonclinical discovery development is a complex process of compound selection that includes *in silico* assessments, in vitro/ex-vivo screening assays and the use of *in vivo* animal models to evaluate on-target pharmacology and compound toxicity. During the discovery stage of topical dermatological drug development for new chemical entities (NCE), initial assessments are conducted on the drug substance, also termed the active pharmaceutical ingredient (API). As a chemical structure is being developed by the chemists for selection of a lead compound with physicochemical parameters suitable for a topical dermatological product, screening studies are used to address toxicity risk in early drug discovery. In addition to screening the API, the drug product/formulation also undergoes a screening approach for early assessment of tolerability and systemic absorption while it is being optimized for clinical use.

Predictive methods using new technologies to detect the potential for adverse events are being increasingly utilized; these methods include computational modeling, *in vitro* assays, genetically modified transgenic *in vivo* models, and the application of toxicogenomics. Most early toxicity

[22] Greene, Nigel, and Russell Naven. "Early Toxicity Screening Strategies." *Current Opinion in Drug Discovery & Development* 12, no. 1 (January 2009): 90–97.

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screening strategies use a combination of *in silico* and *in vitro*/*ex vivo* methods with demonstrated predictive capabilities that are also cost effective. The strategies utilized vary throughout the pharmaceutical industry and academia, depending on the risk level, budget and resources available within the institution during the early stages of drug development.

In silico prediction computational approaches based on structural alerts are often used by chemists to screen chemotypes and predict chemical toxicity in the early discovery stages.[23] Using the structure activity relationship (SAR) approach early in discovery enables researchers to quickly identify potential toxic compounds and key alerting substructures and to understand how to modify them in order to synthesize safer molecules. Compared with experimental *in vitro* assays or *in vivo* animal models, these approaches are also less expensive and save time. Chemical mutagenicity is one of the most widely studied endpoints for structural alerts. Derek Nexus and Genetox Expert Alerts from Leadscope are two representatives of commercial expert systems to predict toxicity. Several other automated detections of SAR are being developed in computational toxicology, and there are many excellent methods and toolkits available. Evaluation of these methodologies has been compared and evaluated in terms of their capability in identification of structural alerts using Ames mutagenicity data sets as a benchmark.[24] All the methods are widely available and readily applicable. Although these assays provide acceptable accuracy and good capability in identification of significant structural alerts, they can contain many redundant patterns and false positives; therefore, these *in silico* assessments are generally followed up with *in vitro* screening assays and use of a weight of evidence approach.

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[23] Bendels, Stefanie, Caterina Bissantz, Bernhard Fasching, Grégori Gerebtzoff, Wolfgang Guba, Manfred Kansy, Jacques Migeon, et al. "Safety Screening in Early Drug Discovery: An Optimized Assay Panel." *Journal of Pharmacological and Toxicological Methods* (July 5, 2019), 106609. https://doi.org/10.1016/j.vascn.2019.106609.

[24] Yang, Hongbin, Jie Li, Zengrui Wu, Weihua Li, Guixia Liu, and Yun Tang. "Evaluation of Different Methods for Identification of Structural Alerts Using Chemical Ames Mutagenicity Data Set as a Benchmark." *Chemical Research in Toxicology* 30, no. 6 (2017): 1355–64. https://doi.org/10.1021/acs.chemrestox.7b00083.

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In Vitro *Testing*

Genotoxicity testing of drugs is mandatory in preclinical safety testing, but the standard set of assays conducted to meet regulatory requirements is not suitable for high-throughput screening. Several high-throughput *in vitro* screening assays exist and are well established for detecting genotoxic compounds. These assays require only milligrams of test material and significantly decrease the time needed to get results. Genotoxicity screening assays are generally based on the Ames test system and provide fast methods to identify genotoxic agents through multiple technologies that enable numerous compounds to be evaluated during the early chemotype selection phase. Examples of such assays include the GreenScreen HC™ and Bioluminescent Ames assays. GreenScreen is a fast, high-throughput method that identifies genotoxic agents through the detection of gene expression through the GADD45a-GFP reporter system, and detects genotoxic damage in the human lymphoblastoid TK6 cell line.[25] The mini-Ames assay is a modification of the traditional Ames assay to permit the assay to be used as a high-throughput screening assay that requires very small amounts of test material and is based on the detection of the presence or absence of mutants in each of the many microwells as measured by cell growth. This assay detects both frameshift and base-pair substitutions under both nonactivation and exogenous (S9) metabolic activation conditions. Frameshift mutations are detected using the traditional TA98 Salmonella strain. The different types of base-pair substitutions are detected utilizing Salmonella typhimurium strains. The advantages of these high-throughput systems include the use of low amounts of test compound, the ability to automate, they provide high specificity and high sensitivity, they pick up multiple classes of genotoxicity, and they provide nonactivation and S9 metabolic activation conditions.[26]

In addition to early safety screening for genotoxicity, medium to high-throughput assays are also available to screen for cardiotoxicity,

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[25] Hastwell, Paul W., Li-Leng Chai, Kevin J. Roberts, Thomas W. Webster, James S. Harvey, Robert W. Rees, and Richard M. Walmsley. "High-Specificity and High-Sensitivity Genotoxicity Assessment in a Human Cell Line: Validation of the GreenScreen HC GADD45a-GFP Genotoxicity Assay." *Mutation Research* 607, no. 2 (September 5, 2006): 160–75. https://doi.org/10.1016/j.mrgentox.2006.04.011.

[26] Jagger, Christopher, Matthew Tate, Paul A. Cahill, Chris Hughes, Andrew W. Knight, Nicholas Billinton, and Richard M. Walmsley. "Assessment of the Genotoxicity of S9-Generated Metabolites Using the GreenScreen HC GADD45a-GFP Assay." *Mutagenesis* 24, no. 1 (January 2009): 35–50. https://doi.org/10.1093/mutage/gen050.

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hepatotoxicity, and off-target pharmacological activity. These assays are designed to be incorporated into the drug discovery process at a very early stage to design out risk factors during lead optimization of the drug substance and drug product.

Off-target binding toxicities, pharmacologically-based liabilities, and effects on drug-metabolizing enzymes can be understood in early stage drug discovery development by using cell microarrays or receptor binding high throughput screens (CEREP, eXP, Panlabs). By understanding the potential toxic liabilities of a candidate compound, considerable time and resources can be saved in reducing the risk through more informed safety assessment.

Assays for evaluation of cardiotoxicity include the *in vitro* hERG and sodium and calcium channel blocker assays. HERG channels are involved in cardiac action potential repolarization; inhibition of the hERG channel results in lengthening of ventricular action potential, prolonging the QT interval in an electrocardiogram, which increases the risk of potentially fatal ventricular arrhythmias. A number of hERG assays are available, ranging from high-throughput binding assays on stably expressed recombinant channels to electrophysiological examinations in cardiac myocytes.[27] Single-cell manual patch clamp to high throughput, automated electrophysiology assays are available platforms to provide testing for potential cardiac ion channel-related adverse effects.

Drug-induced liver injury (DILI) is a leading cause of acute liver failure and one of the main causes of withdrawal of drugs from the market. Therefore, determining the potential for hepatotoxicity and hepatic injury early in drug discovery development is an important aspect of identifying compounds as potential hazards.[28]A challenge in using *in vivo* animal models for screening of DILI is the differences between species in terms of liver function and chemical metabolism. *In vitro* toxicity tests have been developed and validated as replacements for animal testing in consideration for animal welfare. The precise mechanisms by which a drug can cause DILI are not well understood; however, several hypotheses exist that include roles for mitochondrial dysfunction, reactive metabolites, and immune-

[27] Priest, Birgit T., Ian M. Bell, and Maria L. Garcia. "Role of HERG Potassium Channel Assays in Drug Development." *Channels (Austin, Tex.)* 2, no. 2 (April 2008): 87–93. https://doi.org/10.4161/chan.2.2.6004.

[28] Weaver, Richard J., Eric A. Blomme, Amy E. Chadwick, et al. "Managing the challenge of drug-induced liver injury: a roadmap for the development and deployment of preclinical predictive models." *Nat Rev Drug Discov* (2019). doi:10.1038/s41573-019-0048-x.

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mediated liver injury. The complexity of the underlying biology of liver injury has resulted in selectivity and specificity issues that have hindered the development of in vitro systems for the early detection of hepatotoxicants. Reactive metabolite assays that measure the level of drug-protein adduct formations have been suggested as a simple screen to measure the potential for adverse drug reactions. Similarly, dysfunction of bile acid transporters such as the bile salt excretory pump (BSEP) have been implicated in cholestasis, and inhibition of these transporters by certain drugs may lead to liver injury. Assays have been developed to measure the effects of drugs on these bile acid transporters. However, in isolation, these assays may falsely identify some non-hepatotoxicants as causing liver injury. In such a case, further investigations would be required before making any decision to proceed with development of a compound. Recent reports suggest that the simultaneous measurement of multiple signals linked to key mechanisms of liver injury, such as an assay system using primary human hepatocytes that maintain the differentiated functions of liver metabolism and transport,[29] has the potential to improve the differentiation of hepatotoxicants from non-hepatotoxicants. Using high content imaging techniques and the measurement of parameters such as reactive oxygen species, glutathione, and mitochondrial membrane potential, it is also possible to differentiate hepatotoxicants from non-hepatotoxicants. Although no specific screening paradigm or platform of high-throughput assays has been standardized, there are a vast number of validated assays available. Hepatotoxicity screening tests should be used early in drug discovery to reduce the risk of adverse drug effects on the liver.

General cytotoxicity or cell viability assays that measure the capacity of a chemical to cause an increase in cell death or proliferation have long been employed as surrogate models for *in vivo* toxicity. Depending on the assay protocol, some of the most common approaches include measuring the conversion of ADP to ATP in the assay media following the leakage of enzymes upon cell death or measuring the levels of ATP remaining after compound exposure and lysing of the remaining viable cells. Unfortunately, correlations between the ability of a chemical to induce cell death in an *in vitro* assay and its ability to cause a defined toxicity *in vivo* have proven elusive; such assays are therefore rarely used in isolation.

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[29] Bale, Shyam Sundhar, Lawrence Vernetti, Nina Senutovitch, Rohit Jindal, Manjunath Hegde, Albert Gough, William J. McCarty, et al. “In Vitro Platforms for Evaluating Liver Toxicity.” *Experimental Biology and Medicine (Maywood, N.J.)* 239, no. 9 (September 2014): 1180–91. https://doi.org/10.1177/1535370214531872.

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Skin irritation is a main issue for topical dermatological drug development and difficult to evaluate in the early stages due to inability to utilize animals for early screening, complexity in development composition of formulations, uncertainty in the translation of *in vitro*/*in vivo* animal data to humans. The *in vitro* EpiDerm™ Skin Irritation Test developed by the MatTek Corporation is used to predict the clinical skin irritation potential of test substances in the context of identification and classification of skin irritation hazard according to the European Union (EU) classification systems.[30,31] The test consists of a topical exposure of the test chemical to a reconstituted human epidermis model (human-derived epidermal keratinocytes which have been cultured to form a multilayered highly differentiated model of the human epidermis) followed by a cell viability test measured by dehydrogenase conversion of MTT ([3-4,5-dimethyl thiazole 2-yl] 2,5-diphenyltetrazoliumbromide). The test allows for discrimination between category 2 moderate-strong irritants and non-irritants, but does not discriminate between category 2 and category 3 mild irritants.

In vitro permeation testing (IVPT) assays utilize automated flow-through system for testing permeation and penetration using human skin. After exposure, layers of the skin are analyzed to determine where the drug substance resides within the layers of the skin, whether there is accumulation, and whether it is reaching the site of action.[32] The IVPT assay can be utilized as a screening method to rank test substances in order for potential to cause skin irritation, it mimics the human skin barrier and replaces the rabbit model *in vivo*, determines if the drug substance permeates and penetrates the skin, and can provide a pharmacokinetic profile. IVPT is fundamental to understanding the ability of a drug in a specific formulation to reach its intended site of action and elicit its therapeutic effect, providing guidance to formulation development and determining product bioequivalence.

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[30] MatTek Corporation. "Protocol: In Vitro EpiDermTM Skin Irritation Test (EPI-200-SIT)." MatTek Corporation, November 7, 2017. https://www.mattek.com/wp-content/uploads/EPI-200-SIT-Skin-Irritation-Test-Protocol-MK-24-007-0023.pdf.

[31] Cannon, C. L., P. J. Neal, J. A. Southee, J. Kubilus, and M. Klausner. "New Epidermal Model for Dermal Irritancy Testing." *Toxicology in Vitro* 8, no. 4 (August 1, 1994): 889–91. https://doi.org/10.1016/0887-2333(94)90095-7.

[32] Absorption Systems. "In Vitro Permeation Testing (IVPT)." Accessed October 2019. https://www.absorption.com/kc/in-vitro-permeation-testing-ivpt/.

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Bioanalytical Method Development and Validation

Analysis of bioanalytical samples such as plasma and skin tissues from nonclinical dermal studies are an important aspect of dermal safety testing. Although it is optimal for there to be no systemic exposure after dermal administration of a drug product, bioanalytical sampling is necessary to determine levels of drug in the circulation as well as distribution in the tissues. Bioanalysis involves analysis of drugs, metabolites, and/or biomarkers in biological samples. Researchers often forget that an analytical method needs development and validation prior to conduct of a nonclinical study to enable sample analysis. Several steps are involved in the process of method development including protocol development; synthesis of a reference standard; sample collection, preparation, separation, and detection; and completion of method validation.[33] Adequate time to allow for development of methods should be considered prior to start of a nonclinical study.

Species Selection

The minipig is considered the most appropriate species for dermal toxicity testing by the FDA Division of Dermatology and Dental Products based on its morphological and physiological similarities to human skin.[34] Characteristics of porcine skin more closely resemble those of human skin than do the characteristics of other common non-rodent models used in safety evaluation, such as dogs and nonhuman primates. Rabbits and rats both have skin that is much thinner than humans. The rabbit was previously the non-rodent model of choice for dermal evaluations but is seldom used currently because of the poor anatomical and physiological correlation of rabbit and human skin, and the tendency for studies in rabbits to over-predict effects in humans. The minipig is preferred over the domestic pig because of its manageable size. Several strains of minipig are commercially available: Sinclair (Hormel), Yucatan, Hanford, and Göttingen which vary

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[33] Moein, Mohammad Mahdi, Aziza El Beqqali, and Mohamed Abdel-Rehim. "Bioanalytical Method Development and Validation: Critical Concepts and Strategies." *Journal of Chromatography. B, Analytical Technologies in the Biomedical and Life Sciences* 1043 (February 1, 2017): 3–11. https://doi.org/10.1016/j.jchromb.2016.09.028.

[34] Stricker-Krongrad, Alain, Catherine R. Shoemake, Jason Liu, Derek Brocksmith, and Guy Bouchard. "The Importance of Minipigs in Dermal Safety Assessment: An Overview." *Cutaneous and Ocular Toxicology* 36, no. 2 (June 2017): 105–13. https://doi.org/10.1080/15569527.2016.1178277.

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in hair coat and growth patterns. The Gottingen minipig has pale pink skin and non-pigmented hair, which make dermal effects easy to evaluate. Body weight growth rates are slowest in the Gottingen, and most rapid in the Hanford. Based on the pale skin and slow growth rate, the Gottingen is the minipig of choice in many laboratories. Because of the widespread use of minipigs for nonclinical dermal testing, several contract research organizations have established historical control databases. The Gottingen supplier (Ellegaard, Denmark) also has historical data collected over several years, thus making this strain an attractive choice for assessment of dermal absorption, local tolerance, and systemic toxicity following dermal administration of a drug product.

Dose Volume Feasibility Assessment Study

It is a requirement in repeat dose studies testing dermal products to evaluate the maximum feasible concentration of the formulation as well as the maximum feasible dose that can be administered. This ensures assessments of the toxicity and tolerability of the drug product are conducted under maximum usage conditions for the clinical studies as well as established coverage of dose on a mg/day basis. A non-Good Laboratory Practice (GLP) evaluation can be conducted early in a program to establish the maximum dose that can be administered. This is generally done with the vehicle formulation, which should be of similar composition and viscosity of the drug product that includes the test material. An evaluation is generally done using one or two animals during the pretest period of the repeat-dose study. This also enables an early determination of dose volume so that calculations for the test material and drug product requirements can be done for manufacturing of supplies. The dose site is prepared using approximately a 10% BSA, clipping of the site and cleaning using deionized water and/or a mild soap. The assessment is initiated using a small volume of 0.5 mL/kg of product applied and coverage of the dose site is evaluated. If this volume does not completely cover the site, additional volumes of 0.5 mL/kg are added, stepwise, until a volume that adequately covers the dose site but is not excessive (e.g. does not run off or extend beyond the site) is determined. Dose volumes of up to 2.0 mL/kg are generally evaluated to achieve a maximum application.

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Maximum Tolerated Dose and Dose Range-Finding Studies

Evaluation for acute systemic toxicity of a new drug product is part of a standard development program. A typical program for a topically-administered dermal drug product would include single-dose studies to evaluate irritation and systemic toxicity potential and select doses for repeat-dose studies.[35] Single-dose GLP studies with extended examinations (usually for up to 2 weeks) can be used to support single-dose administration to humans in some cases. If no previous information about the toxicity of the test material is available, a preliminary range-finding/maximum tolerated dose study may be conducted in a small number of animals. One or 2 minipigs per sex (or 1 or 2 animals of 1 sex) may be dosed in a sequential (up and down) pattern, with doses increased or decreased based on results of previous doses, to establish doses for further evaluations. The endpoint of these studies may be local effects (for materials with known irritation potential) or systemic effects of the absorbed drug resulting in a maximum tolerated dose (MTD). Frequently, there is no significant absorption, and acute studies of topically administered products are limited to determination of the maximum feasible dose, which is the largest volume that can be administered of the highest concentration of test material that can be manufactured.

Dose range-finding studies or repeat-dose toxicity studies are generally performed once a tolerated dose has been established in the preceding single-dose MTD studies. A range-finding study is a non-GLP study designed to evaluate repeat-dose toxicity in a small number of animals (1 or 2 animals per sex in control and test material–treated groups) for up to 7 days. Routine evaluations (clinical signs, body weight measurements, food consumption evaluations, ophthalmology, electrocardiograms, clinical pathology, organ weight measurements, and macroscopic and microscopic pathology) as well as evaluations of dermal responses may be performed depending on the level of evaluation desired for the drug product. Repeat dose studies up to 14days, 28days, or 3months are considered definitive GLP studies for regulatory purposes and the duration would be determined

[35] Willard-Mack, Cynthia, Thulasi Ramani, and Carol Auletta. “Dermatotoxicology: Safety Evaluation of Topical Products in Minipigs: Study Designs and Practical Considerations.” *Toxicologic Pathology44, no. 3* (2016): 382–390. doi: 10.1177/0192623315622585.

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by the duration of the planned clinical studies. These will be discussed in the next chapter, which outlines Late Stage Drug Development.

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CHAPTER 3

SUPPORT FOR LATE-STAGE CLINICAL STUDIES

Nonclinical Discovery Development – Late Stage

Once a lead drug candidate has been selected to move forward into clinical studies, mandatory regulatory toxicology studies are conducted using protocols that follow good laboratory practices (GLP). These studies include general repeat-dose toxicity, safety pharmacology, reproductive toxicology, and carcinogenicity.

The duration of general repeat-dose toxicity studies is determined by the proposed clinical treatment duration and based on the regulatory guidelines ICH M3(R2) 2010; study durations are generally 14 days, 28 days, 13 weeks, or 9 months, with an additional recovery phase. Reversal is considered appropriate in the earlier studies if known target tissues have been identified and further understanding of their reversal is desired, otherwise a recovery phase can be added on to the subchronic or chronic duration studies. In dermal toxicity studies, a reversal phase is especially useful to monitor any latent effects of the drug product on the skin.

Dermal Toxicity Studies

Dermal toxicity studies conducted in support of topical administration in the clinic and regulatory submissions are routinely performed in the minipig. In addition to the investigational drug product, treatment groups in dermal toxicity studies include a vehicle control utilizing the drug product vehicle (as a "placebo") and a sham control (without vehicle or drug product administration) to enable a comparator for the vehicle against animals that were not treated and only receiving dose site preparations (hair clipping and wiping). Doses administered should provide at least three dose levels utilizing several drug product concentrations similar to the anticipated clinical doses and ensuring that multiples of the human dose on a mg/kg/day, mg/cm^2/day, and exposure basis are achieved. The high dose is generally selected as the maximum feasible concentration and more

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frequent application (e.g. twice a day versus once daily) can ensure exposures are maximized.

Frequency of dermal administration should also be similar to the clinical situation (e.g. once daily or twice daily) and exposures for up to 20 to 22 hours per day, with a period in between dosing to allow removal of residual material from the previous application. Between applications, the skin is washed using deionized water or a mild soap depending on the properties of the drug product formulation. Prior to the start of drug product administration, the application site is prepared by clipping and shaving the hair over the dorsal surface and flanks of the animal to allow for administration over a marked BSA of 10%. This hair clipping procedure is conducted throughout the study as needed based on hair regrowth and marked areas adjusted as the animals grow in order to keep the dose site constant relative to the animals' body weight. In some cases where the drug product is intended for clinical indications with damaged or wounded skin, such as burns or diabetic ulcers, groups of animals with abraded skin can be used after tape stripping or other wounding procedures, if necessary.[36] In the FDA Guidance for Industry, *Chronic Cutaneous Ulcer and Burn Wounds—Developing Products for Treatment*,[37] animal wound models, biodistribution and pharmacokinetic studies, and toxicology studies are described.

Standard parameters in general repeat-dose toxicity studies include body weight measurements, food consumption, clinical observations, hematology and clinical pathology, urinalysis, organ weight, and macroscopic and microscopic evaluations. Dermal scoring for irritation is evaluated routinely using Draize scoring, as discussed in more detail in the section on local safety studies. Due to the propensity for minipigs to rub against the sides of their pens and the non-occlusive administration of the drug product, the potential for cross-contamination of vehicle and sham control animals with the drug product treated animals should be considered. Controls should be treated first followed by test-material treatment groups by ascending dose concentration; technical staff should frequently change protective clothing

[36] Sullivan, T. P., W. H. Eaglstein, S. C. Davis, and P. Mertz. "The Pig as a Model for Human Wound Healing." Wound Repair and Regeneration: Official Publication of the Wound Healing Society [and] the European Tissue Repair Society 9, no. 2 (April 2001): 66–76. https://doi.org/10.1046/j.1524-475x.2001.00066.x.

[37] Food and Drug Administration. *Chronic Cutaneous Ulcer and Burn Wounds – Developing Products for Treatment*. Guidance for Industry. June 2006. https://www.fda.gov/media/71278/download.

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and gloves between dose groups, or even between animals in order to mitigate any issues of cross-contamination. Control animals can be housed in a separate room or separated by an empty pen between control and drug product treated animals.

At necropsy, in-life observations such as erythema, skin discoloration and lesions may not be apparent due to procedures of exsanguination or tissue fixation; the skin should therefore be examined carefully to identify macroscopic findings and correlate them with in-life observations before the skin is collected for processing. Untreated skin should be sampled from the same general body area as treated skin to minimize variations in skin thickness and follicle density and to avoid potential histological differences. If required for toxicokinetic evaluations, full thickness skin samples may be collected to quantitatively assess test material concentrations. These samples should be collected prior to placing the rest of the skin specimen(s) into fixative. The time of necropsy/skin collection should be recorded for each individual animal to better match toxicokinetic plasma exposure to skin exposure.

Skin should be trimmed with the grain of the hair (in the direction of hair growth) to achieve this orientation.[38] In the ideal skin section, hair follicles are oriented vertically along their long axis. This allows the pathologist to evaluate the entire hair follicle and determine its stage in the hair cycle, if necessary. As hair follicles are widely spaced in minipig skin, a large enough skin sample should be taken to ensure that at least a few follicles are present. Drug products are applied to the skin of the dorsum and sides and histologic features of the skin in these regions are of greatest relevance to histopathological evaluation of dermal studies. In the standard application area, the dermis is thick and compact and is composed of tightly interwoven collagen bundles with sparse hair follicles.[39] Many follicles are relatively large and have large erector pili muscles, which are conspicuous features in the dermis. Simple tubular apocrine glands are associated with hair follicles, and their ducts open directly onto the skin surface near follicular orifices. Sebaceous glands are associated with hair follicles in some regions of the

[38] Ruehl-Fehlert, Christine, Birgit Kittel, Gerd Morawietz, Paul Deslex, Charlotte Keenan, Charles Mahrt, et al. "Revised Guides for Organ Sampling and Trimming in Rats and Mice—Part 1A Joint Publication of the RITA1 and NACAD2 Groups". *Experimental and Toxicologic Pathology* 55, no. 2-3 (2003): 91-106. doi:10.1016/s0940-2993(04)70148-7.

[39] Meyer, Wilfried, Klaus Neurand, and Birgitt Radke. "Collagen Fibre Arrangement in the Skin of the Pig". *Journal of Anatomy* 134, no. 1 (1982): 139-148.

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skin. The subcutis can be very extensive, depending on the age and nutritional status of the animal. Additional details about porcine skin are available in the literature.[40,41]

Safety Pharmacology

Safety pharmacology studies are generally required in order to support clinical dosing prior to first time in human phase 1 trials. Regulatory guidance is provided as ICH S7A and S7B.[42,43] The primary organ systems evaluated during safety pharmacology studies include the central nervous system (CNS), cardiovascular system, and respiratory system. Secondary target organ systems can also be evaluated including the gastrointestinal system and the renal system. For dermal drug development, safety pharmacology studies are generally conducted as part of the nonclinical package, in a similar manner to oral new drug entities. The difference in the conduct of these studies is use of the minipig, primarily for the cardiovascular studies, and a rodent (mainly a rat) for the CNS and respiratory studies. Although it is expected that the clinical route of administration is used when feasible, guidance indicates that assessment of effects by another route may be appropriate where there are anticipated significant qualitative and quantitative differences in systemic or local exposures. These studies are usually single dose and expect exposures to produce moderate adverse effects in conscious animals; dermal administration is not therefore recommended, as this limits systemic exposure of the drug to be tested. The drug is administered by the oral, IV, or subcutaneous routes in order to achieve systemic exposures and enable assessment of the onset, duration, and magnitude of potential undesirable pharmacodynamic effects of the drug substance on physiological functions.

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[40] Meyer, W., R. Schwarz, and K. Neurand. “The Skin of Domestic Mammals as a Model for the Human Skin, with Special Reference to the Domestic Pig.” *Skin - Drug Application and Evaluation of Environmental Hazards* 7 (1978): 39–52. https://doi.org/10.1159/000401274.

[41] Montagna, William, and Jeung S. Yun. "The Skin of The Domestic Pig.". *Journal of Investigative Dermatology* 43, no. 1 (1964): 11-21. doi:10.1038/jid.1964.110.

[42] Food and Drug Administration. *S7A: Safety Pharmacology Studies for Human Pharmaceuticals*. Guidance for Industry. July 2001. https://www.fda.gov/media/72033/download.

[43] Food and Drug Administration. *S7B: Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals*. Guidance for Industry. October 2005. https://www.fda.gov/media/72043/download.

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For cardiovascular assessment, evaluations include the hERG assay (potassium channel block), telemeterized minipig study, and ECG evaluations during the general toxicology repeat-dose dermal studies. Cardiovascular studies assess cardiac output, ventricular contractility, vascular resistance, and the effect of endogenously released and/or exogenously administered neurotransmitters on cardiovascular response. CNS studies are generally conducted in rodents and include behavioral pharmacology, learning and memory, visual/auditory and/or electrophysiology examinations, pro-convulsion, and abuse ability. The most common test battery used for CNS evaluations is the Irwin screen or Functional Observational Battery. Respiratory studies may be conducted on rodents or non-rodents and include assessment of respiratory rate and tidal volume or hemoglobin oxygen saturation.

Safety pharmacology studies may not be needed for dermal drug products if the pharmacology of the drug substance is well characterized, and where systemic exposures or distribution to other tissues is demonstrated to be low in humans. Whether or not safety pharmacology studies are required should be discussed with regulatory agencies prior to dosing in humans in order to obtain a waiver for these studies.

Reprotoxicology

Nonclinical reproductive toxicology studies are conducted to evaluate the potential effects of a drug substance on the reproductive and embryo-fetal development parameters to enable enrollment of women of childbearing potential into human clinical trials. Regulatory considerations for reproductive toxicology testing are complex, and several guidelines and reviews are available outlining considerations for these studies.[44,45] Generally, these studies are conducted using a route of administration that

[44] Denny, Kevin H and Ali S Faqi. "Nonclinical Safety Assessment of Developmental and Reproductive Toxicology: Considerations for Conducting Fertility, Embryo-Fetal Development, and Prenatal and Postnatal Developmental Toxicology Studies." In: *Developmental and Reproductive Toxicology.* Humana Press, New York, NY. (2015): 43–115. doi: 10.1007/7653_2015_53.

[45] European Medicines Agency. ICH S5(R3) guideline on reproductive toxicology: detection of toxicity to reproduction for human pharmaceuticals. EMA/CHMP/ICH/544278/1998. August 2018. https://www.ema.europa.eu/en/documents/comments/overview-comments-received-ich-s5-r3-guideline-reproductive-toxicology-detection-toxicity/chmp/ich/544278/1998-revision-3_en.pdf.

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achieves systemic exposures and uses the rat as the primary species and the rabbit as the secondary species due to the extensive historical background data available.

Carcinogenicity

Carcinogenicity studies for dermal drug products should be conducted using dermal administration. Generally, the mouse is used for dermal carcinogenicity studies and, if required, the rat is used as an additional rodent species to evaluate systemic exposure by an alternative route of administration. Conditions relevant for carcinogenicity testing are discussed in the ICH S1A, S1B, and S1C(R2) documents.[46,47,48] These studies are conducted in parallel with clinical phase 3 studies to support the marketing application.

Local Safety

Nonclinical Local Tolerance Assessments

Local tolerance testing is one of the key elements in both nonclinical and clinical safety evaluations of topically-applied dermal drug products. The evaluation of local tolerance should be performed in nonclinical studies prior to human exposure to the product. The purpose of these studies is to ascertain whether the drug product (including both active substances and excipients) is tolerated at the sites of administration on the body. The types of studies to be considered for conducting nonclinical local tolerance testing

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[46] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). *S1A: The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals*. Guidance for Industry. March 1996. https://www.fda.gov/media/71921/download.

[47] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). *S1B Testing for Carcinogenicity of Pharmaceuticals*. Guidance for Industry. July 1997. https://www.fda.gov/media/71935/download.
European Medicines Agency.

[48] European Medicines Agency. *ICH Topic S1C(R2) Dose Selection for Carcinogenicity Studies of Pharmaceuticals*. EMEA/CHMP/ICH/383/1995. October 2008. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-s-1-c-r2-dose-selection-carcinogenicity-studies-pharmaceuticals-step-5_en.pdf.

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of drug products are outlined in the European Medicines Agency Guideline on Non-Clinical Local Tolerance Testing of Medicinal Products.[49]

Tolerance should be determined at those sites that come into immediate contact with the drug product as a result of the method of administration. This should take place before the first trials—with any formulation—in humans. In addition, for those sites that might come into contact through accidental or unavoidable exposure to the product, such as the eye, a nonclinical evaluation for local tolerance should be conducted before clinical trials. The site of administration may be the same organ or tissue that is intended to be the therapeutic target, or the site of administration may be remote from the intended therapeutic target. Therefore, nonclinical local tolerance for several organs will sometimes be tested for a single drug candidate. Local tolerance studies in animal models may be performed as a stand-alone assay/study or may be conducted as part of a repeat-dose, in vivo toxicity study, which is ideal in order to reduce the number of animals as much as possible.

An evaluation of skin reactions in repeat dose toxicity studies, for erythema/eschar and edema is generally performed using a Draize scoring scheme (see Table 3-1). Each animal is assigned separate erythema and edema scores. The most severely affected area within the test site is graded. The Draize Test is an acute toxicity test devised in 1944 by Food and Drug Administration (FDA) toxicologists John H. Draize and Jacob M. Spines.[50] Initially used for testing cosmetics, the procedure involved applying the test substance to the eye or skin of a restrained, conscious animal, and then waiting for a set amount of time before rinsing it off and recording any effects. Because of the controversial nature of this test, use of the Draize test in the US and Europe has declined for ocular irritation testing, but it is still used for evaluation of skin reactions.

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[49] European Medicines Agency. *Guideline on non-clinical local tolerance testing of medicinal products*. CHMP/SWP/2145/2000. October 2015. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-non-clinical-local-tolerance-testing-medicinal-products_en.pdf.

[50] Teixeira, Leandro, and Dubielzig, Richard. 2013. “Eye”. In Haschek and Rousseaux's Handbook of Toxicologic Pathology (Third Edition), edited by Wanda Haschek, Colin Rousseaux and Matthew Wallig, 2095-2185. San Diego: Elsevier Science Publishing Co Inc.

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Table 3-1 Scoring Scale for Evaluating Skin Reactions

Severity Grade	Erythema Definition	Edema Definitions
Grade 0	No erythema	No edema
Grade 1	Very slight erythema (barely perceptible)	Very slight edema (barely perceptible)
Grade 2	Well-defined erythema	Slight edema (edges of area well defined by definite raising)
Grade 3	Moderate to severe erythema	Moderate edema (raised approximately 1 mm)
Grade 4	Severe erythema (beet redness)	Severe edema (raised more than 1 mm and extends beyond the area of exposure)
NOTE: Each animal is assigned separate erythema and edema scores. The most severely affected area within the test site is graded.		

Phototoxicity

Phototoxicity is an acute, light-induced response that occurs when photoreactive chemicals are activated by solar lights and transformed into products cytotoxic against the skin cells. Several symptoms of phototoxicity have been identified, including skin irritation, erythema, pruritis, and edema that are similar to those of an exaggerated sunburn. Both UVB (290~320 nm) and UVA (320~400 nm) are responsible for the manifestation of phototoxicity. Absorption of photons and absorbed energy by photoactive chemicals results in molecular changes or generates reactive oxygen species depending on how endogenous molecules are affected by phototoxicants. Mechanisms of phototoxicity are categorized into two modes of action: Direct when unstable species from excited state directly react with the endogenous molecules, and indirect when endogenous molecules react with secondary photoproducts. The ICH S10 Guideline recommends international standards for photosafety assessments to harmonize such

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assessments supporting human clinical trials.[51] The initial consideration for assessment of photoreactive potential is whether a compound absorbs wavelengths between 290 and 700 nm. Absorption with a molar extinction coefficient (MEC) less than 1000 L mol-1 cm-1 is not considered to result in a photosafety concern. In order to identify the phototoxic potential of a chemical, various test methods have been introduced. Focus is given to animal alternative test methods (e.g.*in vitro*, and *in chemico* assays) as well as *in vivo* methods. The 3T3 neutral red uptake assay, erythrocyte photohemolysis test, and phototoxicity test using human 3-dimensional (3D) epidermis model are examples of in vitro assays. *In chemico* methods evaluate the generation of reactive oxygen species or DNA strand break activity employing plasmid for chemicals or drugs with phototoxic potential.[52]

Sensitization

The Guinea Pig Buehler assay for nonclinical testing of skin sensitization potential is the preferred model by FDA for dermal drug product testing. The clinical formulation should be used for testing and the test material should be the active ingredient in the clinical formulation at concentrations that cover the clinical concentrations. Traditionally, the Guinea pig has been the most commonly used test animal for sensitization studies. Buehler's occluded patch test (without adjuvant) and Magnusson and Kligman's guinea pig maximization test (using adjuvant) have been used for years; both tests measure sensitization as well as elicitation reactions. Multiple variations have been developed, but the basic principles are similar and include topical application and/or intradermal injection of vehicle and test material to groups of animals. Following a one to two week rest period, animals are subsequently re-exposed in an attempt to elicit cutaneous hypersensitivity reactions.

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[51] European Medicines Agency. ICH Guidance S10 on Photosafety Evaluation of Pharmaceuticals. EMA/CHMP/ICH/752211/2012. August 2015. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en.pdf.

[52] Kim, Kyuri, Hyeonji Park, and Kyung-Min Lim. "Phototoxicity: Its Mechanism and Animal Alternative Test Methods." *Toxicological Research* 31, no. 2 (June 2015): 97–104. https://doi.org/10.5487/TR.2015.31.2.097.

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Local Lymph Node Assays

The mouse local lymph node assay (LLNA) developed in 1992 is based on an alternative strategy. The assay provides quantitative data suitable for dose-response assessment and requires fewer animals than the guinea pig sensitization tests. The assay is based on the fact that sensitizers induce a primary proliferation of lymphocytes in the lymph nodes draining the site of application which is called the induction phase of skin sensitization. This proliferation is proportional to the dose applied, and provides objective data on sensitization potentials. Radioactive labeling with (^{3}H) thymidine is done to measure cell proliferation. A minimum of four animals is used per dose group, with a minimum of three concentrations of the test substance, plus a negative control group treated with the vehicle only, and a positive control group, if appropriate. Later modifications of LLNA introduced two nonradioactive modifications and a reduced LLNA approach has been accepted, which could use up to 40% fewer animals. The original LLNA test guideline (OECD TG 429) was adopted in 2002 and updated in 2010.

Bovine Cornea Opacity/Permeability Test (BCOP)

The Bovine Cornea Opacity/Permeability test (BCOP) is an alternative ocular irritation assay designed to replace the rabbit eye test for assessment of eye irritation. The BCOP test method was evaluated by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), in conjunction with the European Centre for the Validation of Alternative Methods (ECVAM) and the Japanese Center for the Validation of Alternative Methods (JACVAM), in 2006 and 2010. It is commonly utilized to test for eye irritation and corrosive potential of test materials that may be used in or around the eye. The BCOP assay is an *in vitro* eye irritation test method developed by Gautheron et al. (1992) that uses living bovine corneal tissue, obtained from non-living animals, to evaluate the potential ocular irritancy of the test material.[53] Types of injury caused by exposure to the test material are quantitatively measured by changes in opacity and permeability to fluorescein. The BCOP assay allows for investigation of the mechanism of the damage caused. Corneal opacity can be caused by protein denaturation or the induction of stromal swelling, while corneal permeability reflects a loss in corneal barrier function and

[53] Gautheron, P., M. Dukic, D. Alix, and J. F. Sina. "Bovine Corneal Opacity and Permeability Test: An in Vitro Assay of Ocular Irritancy." *Fundamental and Applied Toxicology: Official Journal of the Society of Toxicology* 18, no. 3 (April 1992): 442–49. https://doi.org/10.1016/0272-0590(92)90142-5.

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cell-to-cell membrane junctions of the corneal epithelium. An additional histological endpoint can be added to assess the corneal swelling, hydration, or morphological alterations in the cornea. This assessment evaluates the type of observed lesions and the depth of injury into the corneas.

Alternative Assays to Replace Animal Models

A top priority for scientists and regulatory authorities over the years has been the development of alternative methods to replace animals in safety assessments. The OECD is currently evaluating the value of a combination of methods to predict the skin sensitization of chemicals. Factors driving investments in developing non-animal methods include ethical considerations, societal expectations, legislative change, and a general desire to exploit the opportunities provided by new scientific abilities, such as genomics, deep learning, and an improved understanding of the immune system. Many alternative test methods for hazard identification have been developed in the area of skin sensitization; however, the challenge has been a reliable prediction based on a single endpoint readout from these assays. A weight of evidence approach is now therefore the focus in dermal drug development, where multiple *in silico* and *in vitro* assessments are used in the acquisition of skin sensitization data.

Skin sensitization has been described in an adverse outcome pathway with defined key events aiming to increase the mechanistic understanding and interpretation of data and aid in the development of reliable tests. The focus has initially been on the development of *in vitro* methods based on these key events and has resulted in a handful of *in silico* and *in vitro* tests that have been assigned a test guideline by the OECD. Each of these validated assays (Direct Peptide Reactivity Assay (DPRA), human Cell Line Activation Test (h-CLAT), KeratinoSens™, U-SENS™, LuSens, and IL-18 Luc) are single-point tests, yielding very limited, if any, mechanistic insight; therefore, none of the tests have been recognized or proposed as a possible standalone assay to replace the previously used *in vivo* standard, murine LLNA or guinea pig Buehler assay. A new policy on defined approaches for skin sensitization is available for public comment from the EPA; it outlines the history of non-animal models for skin sensitization, evolution of regulatory guidelines pertaining to skin sensitization testing,

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and proposed defined approach to testing using strategies to increase accuracy and sensitivity by different ways of combining existing tests.[54]

Clinical Skin Tolerability Assessments

Irritation and/or sensitization reactions, in addition to being unpleasant for the patient, may result in treatment noncompliance and/or changes in skin permeability leading to an altered rate and extent of drug absorption from the application. It is therefore important to evaluate the local safety of a new topical product during development for both new chemical entities and new formulations.

The FDA held a public workshop in 2018 to discuss the current state and future directions for collection of human data on potential skin irritation with the use of medications applied topically.[55] Conducting tolerability assessments during the late-stage clinical trials in the target population may be sufficient, and specific studies may not always be required. The following initially explains the established dermal safety testing in healthy volunteers, and then, new trends to assess dermal safety in the target population.

Human dermal safety testing has historically referred to provocative testing studies conducted in healthy volunteers. Human dermal safety testing comprises studies to evaluate the potential for cumulative irritancy, contact sensitization, photoirritation (phototoxicity), and photoallergenicity (photocontact allergy). The initial draft FDA Guidance for Industry for Acne Vulgaris (2005) (which was superseded by the final guidance in 2018[56]) outlined topical safety considerations for cumulative irritancy (at least 30 evaluable subjects), contact sensitization (at least 200 evaluable

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[54] Environmental Protection Agency. Interim Science Policy: Use of Alternative Approaches for Skin Sensitization as a Replacement for Laboratory Animal Testing. Draft for Public Comment. April 2018. Office of Chemical Safety and Pollution Prevention. https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OPP-2016-0093-0090&contentType=pdf.

[55] Food and Drug Administration. *Human Dermal (Skin) Safety Testing for Topical Drug Products: Regulatory Utility and Evaluation; Public Workshop; Request for Comments*. Silver Spring, Maryland; September 2018. https://www.fda.gov/drugs/news-events-human-drugs/human-dermal-skin-safety-testing-topical-drug-products-regulatory-utility-and-evaluation-public.

[56] Food and Drug Administration. *Acne Vulgaris: Establishing Effectiveness of Drugs Intended for Treatment*. Guidance for Industry. May 2018. https://www.fda.gov/media/71152/download.

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subjects), phototoxicity (at least 30 evaluable subjects), and photocontact allergy potential (at least 50 evaluable subjects). Dermal provocative irritation studies may be waived if phase 2 safety data demonstrate that the product is irritating, and the Agency determines that this information is adequate for labeling purposes. Phototoxicity and photosensitization studies may be waived if there is no absorption of the drug product by UVB, UVA, or visible light (290 to 700 nm). This should be agreed with the FDA during development, and prior to phase 3. These trials are usually conducted simultaneously with phase 3 clinical trials, although preliminary dermal safety evaluations could be conducted during development of the to-be-marketed formulation.

Guidance for S10 Photosafety Evaluation of Pharmaceuticals has been issued by both the FDA and EMA.[57,58] Phototoxicity is defined as an acute light-induced tissue response to a photoreactive chemical and photoallergy is defined as an immunologically-mediated reaction to a chemical, initiated by the formation of photoproducts (e.g. protein adducts) following a photochemical reaction. For a chemical to demonstrate phototoxicity and/or photoallergy, the following characteristics are critical: absorbs light within the range of natural sunlight (290 to 700 nm); generates a reactive species following absorption of UV-visible light; or distributes sufficiently to light-exposed tissues (e.g. skin, eye). If one or more of these conditions are not met, a compound will usually not present a concern for direct phototoxicity. However, increased sensitivity of skin to light may also occur through indirect mechanisms.

When conducting photosafety studies, irradiation of the exposed area should take place at a specified time after application, and the interval between application and irradiation should be justified based on specific properties of the formulation to be tested. Signs of phototoxicity should be assessed based on relevant endpoints. The sensitivity of the assay should be demonstrated using appropriate reference compounds. If a clinical photosafety assessment is warranted for a topically-applied dermal drug product, there are various options for collecting human data, ranging from

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[57] Food and Drug Administration. *S10 Photosafety Evaluation of Pharmaceuticals*. Guidance for Industry. January 2015. https://www.fda.gov/media/85076/download.
[58] European Medicines Agency. ICH Guidance S10 on Photosafety Evaluation of Pharmaceuticals. EMA/CHMP/ICH/752211/2012. August 2015. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en.pdf.

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reporting of adverse events to a dedicated photosafety trial. Available data on the phototoxicity of chemical class-related compounds could inform the best approach. Reconstructed human skin models may be used to assess the phototoxicity potential of clinical formulations. Under adequate test conditions, a negative result in a reconstructed human skin assay indicates that the direct phototoxicity potential of the formulation may be regarded as low. A negative result in an appropriately conducted *in vivo* animal phototoxicity study may also be sufficient evidence that the formulation is not directly phototoxic. In either case, generally no further clinical phototoxicity testing is recommended.

The FDA Guidance for "Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs" (draft October 2018), applies to generic drugs.[59] Applicants should perform a comparative assessment of the test and reference products using an appropriately designed irritation/sensitization study with humans to demonstrate the potential reaction (reference no worse than test). In a test situation, the product should be studied in a relatively small population (at least 200 evaluable subjects for sensitization) under relatively provocative conditions to maximize the potential for the occurrence of a reaction. The Guidance recommends that skin irritation and sensitization be evaluated in a single study as long as a sufficient number of subjects are included to evaluate sensitization. The recommended study consists of two phases: a 21-day induction phase, followed by a 14- to 17-day rest period, and then a challenge phase. During the induction phase, the test and reference products are applied at contralateral locations of the same anatomical site (based on the reference product labeling). During both the induction and challenge phase, the subject's skin should be scored according to scales provided in the Guidance. Consult ClinicalTrials.gov (U.S. National Library of Medicine) for numerous examples of local safety studies for topical and transdermal drug products, as well as cosmetics.

For topical drug products in general, the clinical to-be-marketed formulation should be tested because changes in formulation may change the irritation potential and/or change the rate and extent of absorption. The intended clinical conditions of administration should be used to the extent

[59] Food and Drug Administration. *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery System for ANDAs*. Draft Guidance for Industry. October 2018. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en.pdf.

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possible. In recent years, the clinical relevance of local dermal safety studies for product labeling has been re-evaluated with respect to occluded application (*vs* non-occluded clinical use), application to intact skin (*vs* clinical use on affected skin), location (patch application vs diseased areas), study sample size, and study duration.

In a FDA Human Dermal Safety Testing Workshop (September 2018),[60] "label-worthy" (true and relevant for using the product safely and effectively) information was presented by Jonathan Wilkin, MD (former FDA director of the Division of Dermatology and Dental Products) for discussion and proposed that characterization of potential allergic contact dermatitis (ACD) to the chronic use studies should provide "label-worthy" information not provided by current acute patch-testing methods. This information would include the frequency of ACD in patients with the relevant skin condition instead of only volunteers with healthy skin, the time of onset, time course for the reaction, and severity of ACD. If the product is not intended for chronic use, patch testing is recommended and the label clearly stating that ACD sensitization has not been evaluated for periods of exposure longer than 21 days. A post-marketing commitment to complete a 6-month, chronic safety study for ACD may be required. For a new chemical entity being developed for a non-serious medical condition, or if the topical product contains a novel inactive ingredient, consider using the current proposed sensitization patch-testing method. Consider empirical data for irritant contact dermatitis with discussion at an end of phase 2 meeting to confirm that the phase 3 safety and efficacy studies will sufficiently inform the potential for irritancy under labeled use conditions on diseased skin.

Although the path forward is trending towards assessing dermal safety during clinical use on affected skin, there is no standardized scoring system or protocol to evaluate irritation and sensitization within a late stage clinical trial. Historically, sponsors used similar, but not standardized, tolerability (irritation) scoring systems. For example, 4- or 5-step scales for investigator assessments of dryness, erythema, and peeling, and 4- or 5-step scales for patient assessments of burning/stinging and itching. The description of each grade varies widely or may not even exist. Recent FDA views on patient

[60] Food and Drug Administration. *Human Dermal (Skin) Safety Testing for Topical Drug Products: Regulatory Utility and Evaluation; Public Workshop; Request for Comments*. Silver Spring, Maryland; September 2018. https://www.fda.gov/drugs/news-events-human-drugs/human-dermal-skin-safety-testing-topical-drug-products-regulatory-utility-and-evaluation-public.

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assessments indicated these should be categorized as patient-reported outcome (PRO) measures; the sponsor should therefore use an established PRO scale, such as itch NRS or pain NRS with 11 steps (0 to 10). It is up to the sponsor to choose what kind of systems to use for measuring tolerability through phase 2 studies, but at the end of the phase 2 meeting, the sponsor should agree with the FDA on how to assess tolerability during phase 3 studies.

It is operationally challenging to conduct patch testing. Training the investigators in the assessment criteria and evaluation process is critical to achieving consistent results. Although most dermatologists learned how to perform patch testing during their residency program, the test is unfavorable in regular clinical practice, and the sponsor should not expect most investigators to be experienced with these methods. For this reason, dermal safety studies are often conducted at specialty clinical research sites that have experience with patch-test studies.

Local Safety Conclusions

Local tolerance testing is a critical aspect of dermal drug development as it is important to evaluate the clinical formulation for the potential to cause skin irritation, sensitization, phototoxicity, or ocular irritation. Although the studies can be extensive and increase drug development costs, they are necessary to ensure that the safety and efficacy of the drug product is not impacted. Local tolerance testing is a continually evolving field both nonclinically, in efforts to follow 3Rs principles (replacement, reduction, refinement), and clinically, to maximize output in patient studies. Collaborative discussions with the regulatory agencies are therefore recommended early in development to ensure the most effective approach.

Additional Considerations

Biomarkers

Biomarker, gene expression, and pharmacodynamic endpoints, measured in the blood or in skin biopsies, may be useful in understanding the mechanism of action of the drug product in early studies, and may be useful in understanding and predicting the potential for treatment success when included in late stage trials. Biomarker endpoints for psoriasis (e.g. IL-17, IL-23) and atopic dermatitis (e.g. IL-4, IL-13, IL-22) are actively explored and are often incorporated into early human studies to guide dose rationale, as well as for corporate Go/No-Go decisions for further development. The

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time course for changes in biomarkers may precede the resolution of clinical symptoms. A heatmap approach is particularly useful to visually assess the upregulation and downregulation of multiple genes over time, comparing changes from active treatment versus placebo, and differences in lesional skin versus nonlesional (i.e. healthy looking) skin. While it may be difficult to establish pharmacokinetic/pharmacodynamic or exposure-response relationships at the site of action, exposure in the interstitial fluid in the dermis, as well as the biological response, may be measured by novel techniques such as dermal open-flow microperfusion (dOFM) and microdialysis. Pharmacokinetics/pharmacodynamics in animal models, where available, can be utilized to establish proof of mechanism and to inform exposure needed at the site of action.

Techniques for collecting drug and biomarkers at the site of action in the skin of humans have evolved, but still frequently rely on punch biopsy. A noninvasive adhesive skin collection, such as developed by DermTech (La Jolla, California USA),[61] can extract RNA and DNA from stratum corneum samples. Reliable collection of stratum corneum tissue to measure gene expression in skin cancers and inflammatory skin diseases is possible from nearly all locations of the body, with the exception of mucosal surfaces, palmar and plantar surfaces, and areas with excessive non-vellus hair (e.g. scalp). Due to the limited amount of samples from the adhesive skin collection patch, only a limited number of genes can be assessed from the technique. Disease areas that can most benefit from this technique may expand in the future as more information is generated about the genes responsible for particular diseases.

Although examples of quantitative systems pharmacology are emerging,[62,63,64] more examples are needed with respect to dermatological assets.

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[61] DermTech. "Melanoma and Skin Cancer Detection." DermTech. Accessed October 20, 2019. https://dermtech.com/.

[62] Kang E, Frey S, Kudrycki, et al. "Physiological modeling offers a valuable tool in early drug development for acne targets". Presented at the Society of Investigative Dermatology Annual Meeting, Albuquerque New Mexico; May 2014.

[63] Hussey E, Cote-Sierra J, Hofland H et al. "Physiological model to investigate and prioritize targets for psoriasis." Presented at the International Conference of the Inflammation Research Association, Bolton Landing NY; September 2012.

[64] Kang E, Wilde T, Damian-lordache V, et al. Mechanistic and quantitative physiological models for the evaluation and prioritization of dermatology disease

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Patient-Reported Outcomes (PROs)

In an ideal situation, drug effects would be measured by a standardized objective scoring system. For most skin diseases, however, no satisfactory objective marker of disease activity is available. Many clinician-reported outcome scales have emerged that incorporate different aspects of disease.[65] These scales, such as the Investigator Global Assessment (IGA) and Eczema Area and Severity Index (EASI) for atopic dermatitis, may appear to be objective because they are recorded by a clinician or an observer rather than the patient, but some subjectivity still influences the results. Although many symptoms of dermatologic conditions, such as pruritus, burning, and sleep disturbance, can only be assessed by the patient, patient-reported outcomes (PROs) have not been commonly reported in dermatologic clinical trials. Previously, pharmaceutical companies have viewed the benefit of including PROs in drug development largely in terms of their potential to secure product labeling or to support value propositions for reimbursement.[66] This environment is changing.

The inclusion of PROs enables regulators to evaluate potential product benefits with a patient-centered perspective. FDA's Patient-Focused Drug Development Initiative is a commitment under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) to more systematically gather and report patients' perspectives on their condition and available treatment options. It is anticipated that more PROs will be created and applied during future clinical trials.

The FDA Guidance for Industry outlines the evaluation principles.[67] The FDA will review documentation of PRO instrument development (conceptual framework, content validity, and other measurement properties) in conjunction

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targets. Presented at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) Annual Meeting, Indianapolis, Indiana; March 2013.

[65] Townshend, A. P., C.-M. Chen, and H. C. Williams. "How Prominent Are Patient-Reported Outcomes in Clinical Trials of Dermatological Treatments?" *The British Journal of Dermatology* 159, no. 5 (November 2008): 1152–59. https://doi.org/10.1111/j.1365-2133.2008.08799.x.

[66] Copley-Merriman, Catherine, Susan Zelt, Marci Clark, and Ari Gnanasakthy. "Impact of Measuring Patient-Reported Outcomes in Dermatology Drug Development." *The Patient* 10, no. 2 (2017): 203–13. https://doi.org/10.1007/s40271-016-0196-6.

[67] Food and Drug Administration. *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. Guidance for Industry. December 2009. https://www.fda.gov/media/77832/download.

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with clinical trial results to determine whether a labeling claim is substantiated. PRO instrument development is an iterative process and involves both qualitative and quantitative validation. Psychometric analyses are generally required to determine if there is a correlation with other measurements (such as gravimetric sweat production for hyperhidrosis) and the clinically meaningful change in scoring. Patient input is critical during instrument development. A PRO should address the severity of the condition as well as the impact on daily living from the patient's perspective. Frequency of administration during clinical trials may be daily or weekly, but should be at meaningful time points (e.g. when the condition is expected to be most severe, when most representative of daily life, and when response to treatment is detectable) and not be too burdensome for the patient to complete. Electronic data capture by use of an electronic PRO tool is generally preferred by sponsors and patients. Timelines can be lengthy for development of a validated PRO and should be planned early in development. Data from phase 2 studies is typically used for quantitative analysis; the tool should therefore be ready for inclusion (considering the ages of interest) in phase 2. An endpoint model is also critical for the role that a PRO is intended to play (whether supportive of a physiologic effect or primary evidence). In addition to efficacy, PRO instruments can be used to measure important safety concerns by having symptoms captured by the patient.

There are a number of established PROs that have been used in clinical studies. Some are general, such as the Health-Related Quality of Life (HRQoL) and Short Form-36 Health Survey (SF-36), while others have been developed to address skin conditions, such as the Dermatology Life Quality Index (DLQI). The DLQI was the first dermatology-specific instrument to measure QoL. The index is a validated questionnaire composed of 10 items and was developed in the United Kingdom from the written responses of 120 patients.[68,69] The DLQI is copyrighted, but may be used without clinicians' seeking permission for routine clinical purposes. For

[68] Finlay, A. Y., and G. K. Khan. "Dermatology Life Quality Index (DLQI)--a Simple Practical Measure for Routine Clinical Use." *Clinical and Experimental Dermatology* 19, no. 3 (May 1994): 210–16. https://doi.org/10.1111/j.1365-2230.1994.tb01167.x.

[69] Mori, S., and E. H. Lee. "Beyond the Physician's Perspective: A Review of Patient-Reported Outcomes in Dermatologic Surgery and Cosmetic Dermatology." *International Journal of Women's Dermatology* 5, no. 1 (February 2019): 21–26. https://doi.org/10.1016/j.ijwd.2018.08.001.

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clinical trials, the copyright owners should be contacted before use.[70] Disease-specific scales, such as the Patient-Oriented Eczema Measure (POEM)[71] and Acne Symptom and Impact Scale (ASIS),[72] are also available. Generic numeric rating scales (NRS) and/or visual analogue scales (VAS) may also be used for assessments such as itch and pain. Clinician-reported outcomes, such as the Psoriasis Area Severity Index (PASI), may or may not correlate with the benefit reported by patients using PROs for conditions such as psoriasis.[73] It is therefore important to include both perspectives in clinical trials and to analyze the relationships.

For payers, PRO data may be used in analyses of the cost effectiveness of new treatments. The increasing use of biological therapies has improved outcomes in dermatology, but has also increased the cost of treatment. Given the high cost of new therapies for dermatological diseases, these drugs face reimbursement challenges from payers, who must balance treatment benefits for an individual patient with overall costs.

[70] Dermatology Life Quality Index (DLQI). Accessed October 2019. http://www.bad.org.uk/shared/get-file.ashx?id=1653&itemtype=document.

[71] Charman, Carolyn R., Andrea J. Venn, and Hywel C. Williams. "The Patient-Oriented Eczema Measure: Development and Initial Validation of a New Tool for Measuring Atopic Eczema Severity from the Patients' Perspective." *Archives of Dermatology* 140, no. 12 (December 2004): 1513–19. https://doi.org/10.1001/archderm.140.12.1513.

[72] Alexis, Andrew, Selena R. Daniels, Nathan Johnson, Farrah Pompilus, Somali Misra Burgess, and Julie C. Harper. "Development of a New Patient-Reported Outcome Measure for Facial Acne: The Acne Symptom and Impact Scale (ASIS)." *Journal of Drugs in Dermatology: JDD* 13, no. 3 (March 2014): 333–40.

[73] Schäfer, Ines, Jana Hacker, Stephan Jeff Rustenbach, Marc Radtke, Nadine Franzke, and Matthias Augustin. "Concordance of the Psoriasis Area and Severity Index (PASI) and Patient-Reported Outcomes in Psoriasis Treatment." *European Journal of Dermatology: EJD* 20, no. 1 (February 2010): 62–67. https://doi.org/10.1684/ejd.2010.0815.

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CHAPTER 4

PHARMACOKINETICS FOR TOPICALLY-APPLIED DRUGS

Pharmacokinetics is the study of changes in drug concentrations in the body over time, and is often described as "what the body does to the drug". Pharmacokinetics is the summation of four processes: absorption, distribution, metabolism, and excretion, referred to as ADME. Sponsors are required to submit evidence of *in vivo* bioavailability or provide justification for waiving the requirement (21 CFR 320.21[74]). Following topical administration, drugs must first be released from the formulation and absorbed into the skin, before distribution through the skin tissue and into the circulation. Topical bioavailability and achieving the required drug concentrations at the site of action is a complex interaction that is highly dependent on the characteristics of both the drug substance and formulation, as well as skin characteristics, such as skin barrier function and maturation. Minor changes in formulation can result in significant changes in exposure and impact upon the safety and efficacy of the topical dermatological drug product. Drug metabolism may occur in the skin, but once the drug reaches systemic circulation, its fate is generally the same as if administered by a systemic route.

In vitro metabolism and *in vivo* pharmacokinetics in animal studies, including bioavailability, dose proportionality, time dependence, and metabolism, can be very informative for potential bioavailability and ADME processes in humans, and should be considered when estimating the range of systemic exposure in humans prior to dosing. Nonclinical discovery drug development of topically applied dermal drug products should include assessment of pharmacokinetics by both the systemic and dermal routes of administration. This can be done through the conduct of oral/IV single-dose rodent and non-rodent pharmacokinetic studies to enable understanding of clearance, bioavailability and distribution as well

[74] Food and Drug Administration. "CFR—Code of Federal Regulations Title 21." April 2019. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=320.21.

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as provide data for allometric scaling for human dose predictions. Dermal pharmacokinetic data can be obtained from specific studies including pharmacology efficacy models, formulation tolerability and toxicity studies. *In vitro* studies addressing drug-drug interaction potential, both as a victim as well as a perpetrator, including metabolism and transporter mediated drug-drug interactions should be addressed if systemic exposures are expected in the clinic. The FDA and EMA have outlined the recommended assays and considerations in published guidance documents.[75,76]

A dosing rationale should consider the therapeutic target exposure at the site of action, as well as the potential systemic exposure relative to exposure limits in animal toxicology studies. There are a number of guidance documents addressing first-in-human dosing rationales that vary depending on the study population (e.g. healthy volunteer versus patient with the relevant condition).[77,78]

Pharmacokinetic issues to be addressed during development of a topical drug product include the rate and extent of absorption of the parent drug and any metabolites, safety margins for systemic exposure, variability in pharmacokinetics (both within and between patients), proportionality to the applied dose, drug-drug interaction potential (both as victim and as perpetrator), the effect of patient covariates (such as age, sex, race, body weight), and the exposure-response relationship. Historically, pharmacokinetic assessment for topically-applied dermatological drug products has been restricted by bioanalytical limitations, a lack of understanding factors that may confound study results, a lack of ability to measure local concentrations, and a lack of understanding the correlation of *ex vivo* penetration studies

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[75] Food and Drug Administration. *In vitro Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies*. October 2017. https://www.fda.gov/media/108130/download.

[76] European Medicines Agency. *Guideline on the investigation of drug interactions*. CPMP/EWP/560/95/Rev. 1 Corr. 2. June 2012. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions_en.pdf.

[77] Food and Drug Administration. *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers*. Guidance for Industry. July 2005. https://www.fda.gov/media/72309/download.

[78] European Medicines Agency. *Strategies to Identify and Mitigate Risks for First-in-Human Early Clinical Trials with Investigational Medicinal Products*. EMEA/CHMP/SWP/28367/07 Rev.1. September 17, 2018. https://www.ema.europa.eu/en/strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational-medicinal.

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with systemic exposure. Clinical trials or surrogate endpoints (such as hypothalamic pituitary adrenal axis suppression with potent corticosteroids) have been used to assess potential concerns over safety resulting from systemic bioavailability. As analytical sensitivity has advanced, it is now possible to measure what was once considered "negligible" levels. Bioanalytical assay method development and validation[79] should be started well in advance of clinical trials, with a lower limit of quantitation in the picogram/mL or low nanogram/mL range. Ideally, blood samples for determination of the drug concentration should be collected in early clinical studies to inform the dosing and design of the Maximum Usage Trial (MUsT). The MUsT should not be the first time that pharmacokinetics is evaluated for a new compound or formulation. Even if complete profiles cannot be collected or quantified, sparse concentrations can be used to build a pharmacokinetic model or a physiologically-based pharmacokinetic model (PBPK) to conduct simulations for potential dosing scenarios. Modeling and simulations are useful for estimating the systemic exposure in specific populations (e.g. renal and/or hepatic impairment, elderly, pediatric). Urine collection for determination of the concentrations of the administered drug, excipients, and/or metabolites may also be informative and should be considered in early clinical trials. It is important to consider circulating metabolites and the requirement to follow metabolite concentrations if they account for >10% of the circulating material. It is also important to confirm that circulating metabolites in humans are covered by the toxicology studies as outlined in the FDA Guidance for Industry, Safety Testing of Drug Metabolites.[80]

The actual dose delivered can confound the understanding of systemic pharmacokinetics, as the dose is determined by the concentration/strength of the product, the spreadability of the formulation (cream, gel, ointment, foam), the amount that is applied (typically 1 to 3 mg/cm^2 for a "thin layer," a "pea size," or a "fingertip"), and the BSA (% or cm^2) of the drug product administration site. These variables can vary significantly for a patient in a clinical trial and data may not be captured to allow for an accurate determination of the actual doses applied. A common method of estimating dosing in clinical trials is weighing the drug containers (e.g. tubes) when dispensed to the patient and when returned to the study center; an average daily "dose" will then be calculated. Additional variability can be introduced by

[79] Food and Drug Administration. *Bioanalytical Method Validation*. Guidance for Industry. May 2018. https://www.fda.gov/media/70858/download.
[80] Food and Drug Administration. *Safety Testing of Drug Metabolites*. Guidance for Industry. November 2016. https://www.fda.gov/media/72279/download.

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whether the application site is occluded, exposed to air and/or light, and whether the skin is washed before absorption is complete. Studies should include pharmacokinetic collection with the proposed method of application, considering the amount of product applied and the extent of BSA.

Single-dose studies for topical application are of limited value as accumulation in the skin is not usually complete until after at least several daily applications, and a minimum of 7 to 10 days is therefore generally required to reach steady-state (when the rate in, absorption, is equal to the rate out, elimination). Most often, absorption is rate-limiting and is a longer process than elimination (referred to as "flip-flop" pharmacokinetics). For a drug with a long terminal elimination half-life, longer dosing may be required to reach steady-state conditions. It should also be considered if the duration of dosing is sufficient to appreciate a clinical benefit, as the skin barrier will likely change with treatment, which will alter the absorption. Therefore, pharmacokinetic sampling should occur throughout the treatment period, with samples collected on several different days. Measurements of skin barrier function, such as transepidermal water loss (TEWL), may be informative and included as a covariate when analyzing the systemic exposure.

Maximum Usage Trials

A recent (July 2019) FDA public workshop[81] was held to discuss Topical Drug Development - Evolution of Science and Regulatory Policy, which included a presentation of current thinking on the MUsT design. MUsTs have been required since the early 1990s for prescription drugs to be approved by an NDA, and more recently are also required for over-the-counter (OTC/nonprescription) products. The FDA recently issued the Guidance for Industry "Maximal Usage Trials for Topically Applied Active Ingredients Being Considered for Inclusion in an Over-The-Counter Monograph: Study Elements and Considerations".[82] A guidance for

[81] Food and Drug Administration and University of Maryland. Public Workshop, "Topical Drug Development – Evolution of Science and Regulatory Policy." Baltimore, Maryland, July 2019.
https://www.pharmacy.umaryland.edu/centers/cersievents/topical/.

[82] Food and Drug Administration. *Maximal Usage Trials for Topically Applied Active Ingredients Being Considered for Inclusion in an Over-The-Counter Monograph: Study Elements and Considerations*. Guidance for Industry. May 2019. https://www.fda.gov/media/125080/download.

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prescription drugs has not yet been issued; however, Bashaw et al published an overview of design considerations for systemic bioavailability trials for topical dermatological products.[83]

The MUsT design should include factors representative of the maximum expected exposure for the drug product:

1) Patients with the relevant dermatologic condition, rather than healthy volunteers
2) Frequency of dosing
3) Duration of dosing
4) Use of the highest proposed strength
5) Total involved surface area to be treated at one time
6) Amount of drug product per area of application
7) Application method and site preparation
8) Product formulation (to-be-marketed formulation should be used)
9) Validated bioanalytical method with adequate sensitivity

The MUsT has also been referred to as a maximal use pharmacokinetics trial and was initially included in the 2005 "Draft Guidance for Industry: Acne Vulgaris - Development Drugs for Treatment ".[84] The MUsT is an assessment of systemic exposure that is relevant for systemic safety. Recruitment of patients at the upper end of the anticipated BSA involvement and dosing with the highest concentration/strength to be marketed and/or studied in phase 3 is a requirement of the MUsT design to increase the chances of demonstrating systemic exposure concentrations. For all indications, consideration should be given to the maximum %BSA that will

[83] Bashaw, Edward Dennis, Doanh C. Tran, Chinmay G. Shukla, and Xiaomei Liu. "Maximal Usage Trial: An Overview of the Design of Systemic Bioavailability Trial for Topical Dermatological Products." *Therapeutic Innovation & Regulatory Science* 49, no. 1 (January 2015): 108–15. https://doi.org/10.1177/2168479014539157.

[84] FDA Food and Drug Administration. Acne Vulgaris: Developing Drugs for Treatment. Guidance for Industry (Draft). 2005. [Note: superseded by final guidance in 2018.]

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be recommended in the product label. The affected %BSA to be treated in the MUsT will vary with condition and age—generally, the requirements are as follows:

- Acne: the entire face, shoulders, upper chest, and upper back should be treated in adults and pediatrics
- Atopic dermatitis: at least 25% in patients 12 years and older; at least 35% in patients below 12 years of age.
- Psoriasis: at least 20% in adults, at least 10% in 12- to 17-year-olds, and at least 3% in patients below 12 years of age.

The MUsT may be a stand-alone trial or a sub-study in a larger phase 2 or 3 trial in patients with the intended condition. If the studied condition will make it difficult to collect pharmacokinetic samples (e.g. epidermolysis bullosa), then a waiver may be justified. In some cases, such as alopecia and vitiligo (pigmentation disorders) where the skin is considered intact, studies in people with healthy skin may be considered acceptable.[85] A MUsT conducted in adults initially, is critical to supporting the pediatric development; studies in younger age groups may be initiated in a step-wise or staggered fashion, depending on the intended population and the safety experience with the product. The disease severity and %BSA for application should be appropriate for each age group. For new chemical entities, where safety margins may be of concern or unknown, a gradual increase in surface area treated may be considered before exposing patients to a maximum dose.

Data from the MUsT are used to support the clinical pharmacology section of the product label, and may also be used to address safety (such as QTc prolongation and safety margins), drug-drug interactions, and use in specific populations. If the systemic exposure is above sub-nanomolar, then a thorough QT (TQT) study is likely to be required, whereas, if exposure is sub-nanomolar and the hERG is negative, then the TQT requirement may be waived. If systemic exposure is anticipated, collecting time-matched ECGs and/or holter monitoring in the MUsT to enable a concentration-QTc slope analysis may be sufficient to address the potential of the drug for QTc prolongation. A recent scientific white paper addressing concentration-QTc

[85] Food and Drug Administration and University of Maryland. Public Workshop, "Topical Drug Development – Evolution of Science and Regulatory Policy." Baltimore, Maryland, July 2019.
https://www.pharmacy.umaryland.edu/centers/cersievents/topical/.

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modeling describes the requirements to address the potential for QTc interval prolongation of new drugs.[86] There are special situations where the administered drug may not be quantifiable, may be rapidly metabolized or excreted, may be an endogenous compound, or may have a high dietary intake. Novel excipients may also need to be measured.

When planning for the conduct of a MUsT in patients, it is helpful to obtain logistical feedback from potential investigators and clinical trial managers to identify issues that may delay or deter enrollment and participation. It is also highly recommended to seek FDA input into the MUsT study design prior to conduct.

Concentration-time data are generally analyzed by non-compartmental (model-independent) analysis using validated software such as Phoenix WinNonlin (Certara, Princeton, NJ, USA). Pharmacokinetic parameters such as the maximum concentration (Cmax), time of the maximum concentration (tmax), and the area under the concentration time curve (AUC) will be reported. If there are sufficient data to describe elimination, then the half-life (t1/2) may also be calculated, although for topical drugs, the elimination phase may not be evident during a dosing interval, and sampling for several days following the last dose may be necessary to characterize the elimination phase. Volume and clearance parameters can be calculated and will be influenced by the fraction of the dose absorbed (bioavailability). Generally, the tmax will be variable over the dosing interval, and may range from very early after application to the end of the dosing interval (e.g. 12 hours if applied twice daily). In some cases, a compartmental model may be appropriate as determined by assessment of the concentration-time profile. A population pharmacokinetic approach (using nonlinear mixed effects modeling or NONMEM®(ICON Development Solutions, Ellicott City, MD)) may also be used if sparse sampling is included and will provide an opportunity to evaluate the effect of covariates (such as age, sex, race, body weight) on pharmacokinetics. Simulations for different dosing regimens may be generated once a pharmacokinetic model has been established. PBPK modeling may be used for more complex models to gain a mechanistic understanding of

[86] Garnett, Christine, Peter L. Bonate, Qianyu Dang, Georg Ferber, Dalong Huang, Jiang Liu, Devan Mehrotra, et al. "Correction to: Scientific White Paper on Concentration-QTc Modeling." *Journal of Pharmacokinetics and Pharmacodynamics* 45, no. 3 (2018): 399. https://doi.org/10.1007/s10928-017-9565-6.

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transdermal absorption and to predict pharmacokinetics under various conditions. More development is needed in this area.

The MUsT may provide an opportunity to support a "repurposed" product (505(b)(2)) application if conducted as a relative bioavailability study with the reference listed drug (RLD). Even if the tested product is not bioequivalent to the RLD, pharmacokinetic parameters, such as the Cmax and area under the concentration time curve (AUC), may provide evidence for a clinical bridge for safety and risk/benefit assessment, especially if the systemic exposure is lower for the test product than the RLD. If exposure of the test product is higher than the RLD, additional safety evidence may be required.

The difference between NDA studies and OTC studies is that the NDA trial focuses on the safety and efficacy of a single drug product, while the goal for OTC is to establish an OTC monograph, determining the conditions under which any of the multiple drug products would be generally recognized as safe and effective. Sunscreens and antiseptics have been the initial focus of the guidance. For OTC products, and specifically for the development of a nonprescription/OTC sunscreen monograph,[87] Matta et al[88] evaluated the plasma concentrations of sunscreen active ingredients. Participants were randomized to 1 of 4 commercially available sunscreens: 2 mg of sunscreen per 1 cm^2 was applied to 75% of the BSA 4 times a day for 4 days with blood samples collected over 7 days. The Cmax of avobenzone was considered the primary endpoint, while the Cmax of oxybenzone, octocrylene, and ecamsule were secondary. The plasma concentrations of all 4 sunscreens exceeded the threshold (0.5 ng/mL) established by the FDA for potentially waiving nonclinical toxicology studies for sunscreens.[85] While the results do not suggest that individuals should refrain from the use of sunscreens, additional studies are needed to determine the clinical significance of the systemic exposure.

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[87] Food and Drug Administration. *Sunscreen Drug Products for Over-the-Counter Human Use*. Proposed rule. Federal Register February 2019. https://www.federalregister.gov/documents/2019/02/26/2019-03019/sunscreen-drug-products-for-over-the-counter-human-use.

[88] Matta, Murali K., Robbert Zusterzeel, Nageswara R. Pilli, Vikram Patel, Donna A. Volpe, Jeffry Florian, Luke Oh, et al. "Effect of Sunscreen Application Under Maximal Use Conditions on Plasma Concentration of Sunscreen Active Ingredients: A Randomized Clinical Trial." *JAMA* 321, no. 21 (04 2019): 2082–91. https://doi.org/10.1001/jama.2019.5586.

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For OTC products and/or for prescription to OTC switch strategies, patients may apply a topical product more liberally and/or more frequently than initially studied. The concentration/strength may also be lower for the OTC product. This needs to be considered when evaluating the benefit/risk of the product and a MUsT may be required to address the safety margin. Differin Gel (adapalene 0.1%) was the first retinoid approved for OTC use in the US.[89] While the safety and efficacy of Differin Gel was initially established in clinical trials, the OTC approval was supported by post-marketing data, data from consumer studies and a MUsT. The MUsT demonstrated that absorption of adapalene is limited, thus supporting safe use of Differin Gel 0.1% by patients 12 years of age or older.

In conclusion, characterizing the pharmacokinetics early in clinical development will provide the basis for further requirements to address systemic safety and potential for drug-drug interactions. In addition to being required for the product label, the MUsT provides an opportunity for bridging clinical data to nonclinical toxicology and safety margins. For some products, the potential exists to correlate the *in vitro* penetration with *in vivo* absorption, which may be useful to predict human exposure.

Considerations for Generic Topical Drugs, Formulation Bridging, and Topical Bioequivalence

Topical bioequivalence (BE) is a rapidly evolving area. Bioequivalence is a term to describe a drug substance, in two identical dosage forms, that reaches the systemic circulation at the same rate and extent. For most routes of administration, this is characterized when 90% confidence intervals of the ratio of the log-transformed Cmax and AUC falls within 0.80–1.25. For a topically applied drug, concentrations at the site of action (skin), is not readily sampled for these determinations.

[89] Food and Drug Administration. *FDA Approves Differin Gel 0.1% for Over-the-Counter Use to Treat Acne*. July 2016. https://www.fda.gov/news-events/press-announcements/fda-approves-differin-gel-01-over-counter-use-treat-acne.

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The issues of bioavailability and BE have been a topic of discussion for topical drugs for quite some time, in the US as well as Europe.[90,91] Only recently have the tools been developed to adequately characterize the exposure at the target site of action. Skin stripping (removal of skin surface and consecutive layers of stratum corneum cells by adhesive tape) was initially proposed to correlate the drug concentration in the stratum corneum with pharmacodynamic effects for glucocorticoids as an estimate for bioavailability. However, reproducibility is difficult, and only the stratum corneum is accessible (deeper tissues such as the viable epidermis and dermis are not obtainable). Therefore, clinical endpoints or pharmacodynamic measurements, such as the vasoconstrictor or skin blanching assay for topical corticosteroids, have been required while drug release assays have filled the gap for quality control issues (such as batch to batch uniformity and minor process changes in manufacturing). Currently, pharmacodynamic or clinical endpoint studies are the most commonly used studies to demonstrate BE of drugs from topically applied semisolids to support abbreviated NDA (ANDA) filings for generic drug products.[92]

As summarized by Chang et al, comparative clinical trials are used to demonstrate the BE to the RLD for most topical drug products.[93] Clinical endpoints are not without risk as high variability is common and the sensitivity to detect a relevant difference between test product and the RLD needs to be evaluated thoroughly. Given that clinical endpoint bioequivalence

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[90] Miranda, Margarida, João José Sousa, Francisco Veiga, Catarina Cardoso, and Carla Vitorino. "Bioequivalence of Topical Generic Products. Part 1: Where Are We Now?" *European Journal of Pharmaceutical Sciences: Official Journal of the European Federation for Pharmaceutical Sciences* 123 (October 15, 2018): 260–67. https://doi.org/10.1016/j.ejps.2018.07.050.

[91] Miranda, Margarida, João José Sousa, Francisco Veiga, Catarina Cardoso, and Carla Vitorino. "Bioequivalence of Topical Generic Products. Part 2. Paving the Way to a Tailored Regulatory System." *European Journal of Pharmaceutical Sciences: Official Journal of the European Federation for Pharmaceutical Sciences* 122 (September 15, 2018): 264–72. https://doi.org/10.1016/j.ejps.2018.07.011.

[92] Ruela, André Luís Morais, Aline Gravinez Perissinato, Mônica Esselin de Sousa Lino, Paula Silva Mudrik, and Gislaine Ribeiro Pereira. "Evaluation of Skin Absorption of Drugs from Topical and Transdermal Formulations." *Brazilian Journal of Pharmaceutical Sciences* 52, no. 3 (2016): 527–44. https://doi.org/10.1590/s1984-82502016000300018.

[93] Chang, Rong-Kun, Andre Raw, Robert Lionberger, and Lawrence Yu. "Generic Development of Topical Dermatologic Products: Formulation Development, Process Development, and Testing of Topical Dermatologic Products." *The AAPS Journal* 15, no. 1 (January 2013): 41–52. https://doi.org/10.1208/s12248-012-9411-0.

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studies are expensive and often require thousands of patients with the intended condition, few topical dermatological drug generic products are available, even though patents and exclusivities may have expired. The FDA has undertaken a major research initiative to develop a pharmacokinetic study methodology that could work in the skin and has funded research in a number of areas including non-invasive techniques, and has awarded a number of grants to establish alternative methods for evaluating therapeutic and bioequivalence of topical drug products.[94,95]

In some instances, because of the lack of sensitivity of BE studies with clinical endpoints, additional tests (e.g. flux measurement across human skin) may be needed to assure BE and drug product quality. The clinical studies used to support the RLD's regulatory filing are generally the foundation for the design of the clinical endpoint study for the generic drugs. In addition, FDA provides BE recommendations for specific products to guide the pharmaceutical industry to conduct specific studies for regulatory filing.[96] If there is no BE recommendation for the drug product of interest, or sponsors intend to use an alternative study approach for the drug product of interest, it is prudent to consult with the Office of Generic Drugs in the US.

Corticosteroid formulations can be tested clinically using the vasoconstrictor activity (as determined by Stoughton-McKenzie skin blanching test[97,98]) of the steroid to quantitate the "topical bioavailability" results. The

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[94] Guy, Richard H. "Assessing the Skin Pharmacokinetics of Topical Drugs, and the Bio(in)Equivalence of Topical Drug Products, Using Non-Invasive Techniques." Project/Grant Numbers: 1U01FD006533-01 (2018); 5U01FD006533-02 (2019). https://projectreporter.nih.gov/project_info_description.cfm?aid=9710735&icde=0.

[95] Food and Drug Administration. *FY2015 Regulatory Science Research Report: Topical Dermatological Drug Products*. May 2017. https://www.fda.gov/industry/generic-drug-user-fee-amendments/fy2015-regulatory-science-research-report-topical-dermatological-drug-products.

[96] Food and Drug Administration. *Product-Specific Guidances for Generic Drug Development*. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

[97] Stoughton, RB. "Vasoconstrictor Assay – Specific Applications." In *Topical Corticosteroids*, edited by HI Maibach and C Surber. Basel: Karger, 1992. pp 42-53. https://doi.org/10.1159/000419858.

[98] Place, V. A., J. G. Velazquez, and K. H. Burdick. "Precise Evaluation of Topically Applied Corticosteroid Potency. Modification of the Stoughton-McKenzie Assay." *Archives of Dermatology* 101, no. 5 (May 1970): 531–37.

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pharmacodynamic response to the topical corticosteroid preparation is measured by chromameter at various time periods, according to the FDA-published Guidance for Industry.[99] Because of the relatively simple procedure, skin blanching tests may be used as a formulation screening or confirmation procedure in the development of topical steroid preparations. The therapeutic response of TEWL caused by retinoids has been investigated, but is currently not accepted by the FDA.[100] Additionally, for the more potent corticosteroids, systemic exposure may be measured along with hypothalamic pituitary adrenal axis suppression.

Methods to measure drug at the site of action have evolved with the development of novel and advanced techniques such as *in vitro* permeation testing (IVPT), microdialysis (insertion of probes in the dermis to determine unbound concentration), and dermal open-flow microperfusion (dOFM). While these methods have not yet been accepted to support BE in a regulatory filing, they offer great promise for better understanding the pharmacokinetics of topically applied drugs in the relevant layers of the skin (epidermis, dermis) and may eventually offer a route to establish BE of topically applied products. This is also important for formulation changes that may occur during the development of a topical product as even minor changes to a formulation can result in dramatic differences in the absorption profile of a drug and require critical studies (including toxicology studies) to be repeated, often with significant delays in the development of the product. Tools for bridging formulations are therefore needed. The FDA Guidance on Scale-Up and Post Approval Changes (SUPAC-SS)[101] defines three levels of changes: Level 1 (change that does not have any detectable impact on formulation quality and performance); Level 2 (could have an impact); and Level 3 (likely to have a significant impact on formulation quality and performance).

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[99] Food and Drug Administration. *Topical Dermatologic Corticosteroids: In vivo Bioequivalence*. Guidance for Industry. June 1995. https://www.fda.gov/media/70931/download.

[100] Chang, Rong-Kun, Andre Raw, Robert Lionberger, and Lawrence Yu. "Generic Development of Topical Dermatologic Products: Formulation Development, Process Development, and Testing of Topical Dermatologic Products." *The AAPS Journal* 15, no. 1 (January 2013): 41–52. https://doi.org/10.1208/s12248-012-9411-0.

[101] Food and Drug Administration. *Nonsterile Semisolid Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In vitro Release Testing and In vivo Bioequivalence Documentation*. Guidance for Industry. May 1997. https://www.fda.gov/media/71141/download.

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Evolving regulatory considerations for BE include characterization of the formulation. Qualitative (Q1) and quantitative (Q2) are used to describe the sameness of inactive ingredients and quantitative composition, which mitigates the risk of known failure modes related to stability/solubility, potential irritation/sensitization, and the vehicle's contribution to efficacy. Q3 is used to define the same physical and structural characterization and controlling Q3 also mitigates the risk of potential failure. Differences in Q1/Q2/Q3 can affect several factors influencing bioavailability. A request for biowaiver may be considered based on the claim of Q1 and Q2 to the RLD with supporting data to demonstrate acceptable comparative physicochemical characteristics and equivalent *in vitro* release (Q3) to the RLD if a clinical study to show non-inferiority to the RLD is not feasible or not considered necessary. Additionally, *in vitro* release testing (IVRT), IVPT, *in vivo* nonclinical and clinical pharmacokinetics (such as in a MUsT), and modeling and simulations may also provide supporting comparative data for consideration. In some special cases, when there is significant drug absorption, and depending on the site of action, systemic pharmacokinetics can be used to demonstrate BE of topical products. Examples include the FDA recommendation for lidocaine patches in the FDA's draft guidance on lidocaine[102] and the approvals of generic Emla® (lidocaine-prilocaine) topical creams. However, in general, the usefulness of pharmacokinetic studies in dermatological drug product evaluation and determination of equivalence is limited.[103]

A draft guidance was recently issued for development of generic acyclovir (5% cream),[104] and at least one generic version of acyclovir 5% cream (Perrigo Company plc) has been approved.[105] The draft guidance

[102] Food and Drug Administration. *Draft Guidance on Lidocaine*. October 2018. https://www.accessdata.fda.gov/drugsatfda_docs/psg/Lidocaine_draft_Topical%20patch_RLD%20020612_RC10-18.pdf.

[103] Chang, Rong-Kun, Andre Raw, Robert Lionberger, and Lawrence Yu. "Generic Development of Topical Dermatologic Products: Formulation Development, Process Development, and Testing of Topical Dermatologic Products." *The AAPS Journal* 15, no. 1 (January 2013): 41–52. https://doi.org/10.1208/s12248-012-9411-0.

[104] Food and Drug Administration. *Draft Guidance on Acyclovir*. December 2016. https://www.accessdata.fda.gov/drugsatfda_docs/psg/Acyclovir_topical%20cream_RLD%2021478_RV12-16.pdf.

[105] Sol-Gel. "Sol-Gel Technologies Announces FDA Approval for Perrigo's Generic Acyclovir Cream, 5%." February 06, 2019. Accessed October 2019. http://ir.sol-gel.com/news-releases/news-release-details/sol-gel-technologies-announces-fda-approval-perrigos-generic.

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allows for two options: an *in vitro* or an *in vivo* study. To qualify for the *in vitro* option, the following criteria should be met:

A. The test and RLD products are qualitatively (Q1) and quantitatively (Q2) the same as defined in the Guidance for Industry *ANDA Submissions - Refuse-to-Receive Standards,* Revision 1 (May 2015).[106]

B. The test and RLD products are physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three lots of the test and three lots (as available) of the RLD product.

C. The test and RLD products have an equivalent rate of acyclovir release based upon an acceptable IVRT comparing a minimum of one lot each of the test and RLD products using an appropriately validated IVRT method.

D. The test and RLD products are bioequivalent based upon an acceptable IVPT comparing the rate and extent of acyclovir permeation through excised human skin from a minimum of one lot each of the test and RLD products using an appropriately validated IVPT method.

Additional comments are provided within the Guidance for Demonstration of Q1 and Q2, the physical and structural comparison, IVRT, and method validation and IVPT comparison. The *in vivo* option is a randomized, double blind, parallel-group, three-arm, placebo-controlled study with a clinical endpoint in healthy, immunocompetent adult males and non-pregnant, non-lactating females with recurrent herpes labialis (cold sores). Due to the modest efficacy demonstrated by the RLD, it is anticipated that a relatively large number of patients would need to be enrolled. The guidance applies only to acyclovir cream 5%; however, the considerations will hopefully be applied to future products following validation, such as was conducted for

[106] Food and Drug Administration. *ANDA Submissions - Refuse-to-Receive Standards*. Guidance for Industry. December 2016. https://www.fda.gov/media/86660/download.

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acyclovir using dOFM[107] and further correlations for IVPT with *in vivo* absorption supplemented by modeling and simulations.

Additional product-specific draft guidances have been developed to outline the studies that should be conducted for a new ANDA. These guidances include less complex, solution-based topical products (e.g. ciclopirox[108] and erythromycin[109] topical solutions), several foam aerosol products (e.g. minoxidil,[110] clobetasol propionate,[111] clindamycin phosphate,[112] ketoconazole,[113] and betamethasone valerate[114]), and moderately complex and complex semisolid topical products.

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[107] Bodenlenz, Manfred, Katrin I. Tiffner, ReingardRaml, Thomas Augustin, Christian Dragatin, Thomas Birngruber, Denise Schimek, et al. "Open Flow Microperfusion as a Dermal Pharmacokinetic Approach to Evaluate Topical Bioequivalence." *Clinical Pharmacokinetics* 56, no. 1 (2017): 91–98. https://doi.org/10.1007/s40262-016-0442-z.

[108] Food and Drug Administration. *Draft Guidance on Ciclopirox*. February 2011. https://www.accessdata.fda.gov/drugsatfda_docs/psg/Ciclopirox_soln_21022_%20RC2-10.pdf.

[109] Food and Drug Administration. *Draft Guidance on Erythromycin*. February 2010. https://www.accessdata.fda.gov/drugsatfda_docs/psg/Erythromycin_SolTopical_%2064187_RC2-10.pdf.

[110] Food and Drug Administration. *Draft Guidance on Minoxidil*. February 2011. https://www.accessdata.fda.gov/drugsatfda_docs/psg/Minoxidil_fmaerosol_OTC_%2021812_RC5-10.pdf.

[111] Food and Drug Administration. *Draft Guidance on Clobetasol Propionate*. February 2011. https://www.accessdata.fda.gov/drugsatfda_docs/psg/Clobetasol_Propionate_fmaerosol_21142_RC2-11.pdf.

[112] Food and Drug Administration. *Draft Guidance on Clindamycin Phosphate*. April 2011. https://www.accessdata.fda.gov/drugsatfda_docs/psg/Clindamycin_Phosphate_fmaerosol_50801_RC04-11.pdf.

[113] Food and Drug Administration. *Draft Guidance on Ketoconazole*. December 2014. https://www.accessdata.fda.gov/drugsatfda_docs/psg/Ketoconazole_fmaerosol_%2021738_RV12-14.pdf.

[114] Food and Drug Administration. *Draft Guidance on Betamethasone Valerate*. December 2014. https://www.accessdata.fda.gov/drugsatfda_docs/psg/Betamethasone_valerate_aerofoam_20934_RC12-14.pdf.

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Methods for Assessing Drug Concentrations in the Skin

There are a number of methods for evaluating drug concentrations in the skin, including microdialysis, blisters, and tape stripping. Additional methods include imaging, tracer studies, and microperfusion.

Microdialysis

Microdialysis allows for measurement of drug concentrations in a tissue using a semipermeable, hollow dialysis probe. Cutaneous microdialysis is a relatively efficient alternative to expensive and larger clinical studies, and allows for determination of a concentration-time profile and calculation of pharmacokinetic parameters (such as clearance) in the skin, although some limitations have been reported for lipophilic and highly bound drugs. Continuous sampling of the free drug in the tissues is the most rational approach to estimate active drug profiles at the site of action, although the sampling time may be limited to less than 10 to 12 hours. Bioequivalence studies of topical formulations may be performed by using microdialysis. Tettey-Amlalo et al evaluated the BE of ketoprofen gels in 18 human subjects by using this technique; AUC results were compared with those of three different commercial products with BE confirmed.[115]

The approval of microdialysis catheters for use in humans opened the door to studies in virtually every human tissue, including muscle, skin, lung, myocardium, brain, and even tumors. In recent years, considerable experience has thus been gained in clinical studies of both healthy volunteers and patients, resulting in more than 2000 publications.[116] The ability of microdialysis to continuously monitor the change of free, unbound drug in the interstitial fluid of different layers of the skin or subcutaneous adipose tissue has made it a valuable tool for investigating these factors. One limitation of microdialysis is that it only measures the drug in the

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[115] Tettey-Amlalo, Ralph Nii Okai, Isadore Kanfer, Michael F. Skinner, Eva Benfeldt, and Roger K. Verbeeck. "Application of Dermal Microdialysis for the Evaluation of Bioequivalence of a Ketoprofen Topical Gel." *European Journal of Pharmaceutical Sciences: Official Journal of the European Federation for Pharmaceutical Sciences* 36, no. 2–3 (February 15, 2009): 219–25. https://doi.org/10.1016/j.ejps.2008.09.002.

[116] Schmidt, Stephan, Rebecca Banks, Vipul Kumar, Kenneth H. Rand, and Hartmut Derendorf. "Clinical Microdialysis in Skin and Soft Tissues: An Update." *Journal of Clinical Pharmacology* 48, no. 3 (March 2008): 351–64. https://doi.org/10.1177/0091270007312152.

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extracellular space, if the site of action is located intracellularly, microdialysis is not therefore able to measure the concentration directly. Even in these cases, the respective extracellular concentration resides closer to the site of interest than the respective plasma or blood concentrations. In addition to assessment of bioavailability (BA) and/or BE, the actual information on free drug concentrations obtained from microdialysis experiments can be further used to predict treatment outcomes. This approach is frequently employed during drug development of anti-infective agents.

Blisters

Similar to microdialysis, the skin blister technique attempts to evaluate tissue distribution through measurement of interstitial drug concentrations.[117] First reported 40 years ago,[118] the basic principle of the technique involves separation of the dermis and epidermis through applied suction on the skin surface. The resulting fluid-filled blisters serve as a surrogate of interstitial fluid. In addition to drug sampling, the technique has also been used to quantify concentrations of endogenous, inflammatory mediators.[119,120] Limitations of this technique include the discomfort resulting from skin blister formation, limited sampling times, difficulties related to

[117] Gonzalez, Daniel, Stephan Schmidt, and Hartmut Derendorf. "Importance of Relating Efficacy Measures to Unbound Drug Concentrations for Anti-Infective Agents." *Clinical Microbiology Reviews* 26, no. 2 (April 2013): 274–88. https://doi.org/10.1128/CMR.00092-12.

[118] Kiistala, U. "Suction Blister Device for Separation of Viable Epidermis from Dermis." *The Journal of Investigative Dermatology* 50, no. 2 (February 1968): 129–37. https://doi.org/10.1038/jid.1968.15.

[119] Day, R. M., M. Harbord, A. Forbes, and A. W. Segal. "Cantharidin Blisters: A Technique for Investigating Leukocyte Trafficking and Cytokine Production at Sites of Inflammation in Humans." *Journal of Immunological Methods* 257, no. 1–2 (November 1, 2001): 213–20. https://doi.org/10.1016/s0022-1759(01)00467-7.

[120] Dearman, Rebecca J., Monica Bhushan, Marie Cumberbatch, Ian Kimber, and Christopher E. M. Griffiths. "Measurement of Cytokine Expression and Langerhans Cell Migration in Human Skin Following Suction Blister Formation." *Experimental Dermatology* 13, no. 7 (July 2004): 452–60. https://doi.org/10.1111/j.0906-6705.2004.00199.x.

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standardization, and the presence of inflammatory proteins and mediators in the blister fluid.[121]

In one example of the utility of blisters, the pharmacokinetics at the target site in bacterial infection of the skin were determined in healthy volunteers following oral administration of ofloxacin.[122] Drug concentrations were determined in suction blister fluid and cantharidin blister fluid, as well as serum and saliva. Favorable penetration into the skin was determined by the high ratios (>1) for blister fluid and serum, and concentrations in the skin above the minimum inhibitory concentrations for bacterial strains of interest.

Tape Stripping

Tape stripping, or the dermatopharmacokinetic method, is a process of sequentially applying and removing tape strips from the skin surface with analysis of the stratum corneum layers collected in each strip. The FDA issued a guidance in 1998 that has since been withdrawn due to inconsistencies and variability in the resulting data. Au et al[123] compared two different commercially available clobetasol propionate cream and ointment formulations using the tape stripping method and demonstrated that the results from tape stripping concur with data from the human skin blanching assay with bioequivalence between the two cream formulations and bio-inequivalence between the cream and ointment. The authors concluded that a well-controlled tape stripping study is an option for the assessment of bioequivalence of topical corticosteroid formulations. The method should be optimized to control sources of variability such as dose

[121] Brunner, Martin, and Oliver Langer. "Microdialysis versus Other Techniques for the Clinical Assessment of *in vivo* Tissue Drug Distribution." *The AAPS Journal* 8, no. 2 (April 14, 2006): E263-271. https://doi.org/10.1007/bf02854896.

[122] Warlich, R., H. C. Korting, M. Schäfer-Korting, and E. Mutschler. "Multiple-Dose Pharmacokinetics of Ofloxacin in Serum, Saliva, and Skin Blister Fluid of Healthy Volunteers." *Antimicrobial Agents and Chemotherapy* 34, no. 1 (January 1990): 78–81. https://doi.org/10.1128/aac.34.1.78.

[123] Au, Wai Ling, Michael Skinner, and Isadore Kanfer. "Comparison of Tape Stripping with the Human Skin Blanching Assay for the Bioequivalence Assessment of Topical Clobetasol Propionate Formulations." *Journal of Pharmacy & Pharmaceutical Sciences: A Publication of the Canadian Society for Pharmaceutical Sciences, Societe Canadienne Des Sciences Pharmaceutiques* 13, no. 1 (2010): 11–20.

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application, removal of residual drug, skin thickness, stripping orientation, and environmental factors.

Cordery et al compared results of the tape stripping method with IVPT studies to assess the bioavailability of three diclofenac topical concentrations (1%, 2%, and 3%) and different dosage forms (solution and gels).[124]Both methods provided similar results. The tape stripping results correlated with the higher performance of one formulation (a 2% diclofenac solution), which had a known permeation enhancer (dimethyl sulfoxide).

Imaging

A number of imaging approaches, such as raman confocal microscopy, MALDI, and FLIM, have promise for understanding disposition of drug in the skin, as well as formulation characteristics.

Raman confocal microscopy

Raman confocal microscopy has contributed to recent advances in the study of skin barrier properties and drug absorption, and is one area of recent research for non-invasive methods. Studies have been limited by signal attenuation in the deep layers of the skin.[125] However, in combination with other approaches, microscopy offers the potential to assess topical BA/BE with novel spectroscopic imaging strategies to enable regulatory science and decision-making.

Stimulated Raman Scattering (SRS) microscopy, a recently developed, chemical imaging tool, is used to acquire high resolution images of multiple chemical components of a topical formulation as it penetrates mammalian skin. This technique uniquely provides label-free, nondestructive, three-dimensional images with high spatiotemporal resolution. It reveals novel features of (trans)dermal drug delivery in the tissue environment: different

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[124] Cordery, S. F., A. Pensado, W. S. Chiu, M. Z. Shehab, A. L. Bunge, M. B. Delgado-Charro, and R. H. Guy. "Topical Bioavailability of Diclofenac from Locally-Acting, Dermatological Formulations." *International Journal of Pharmaceutics* 529, no. 1–2 (August 30, 2017): 55–64. https://doi.org/10.1016/j.ijpharm.2017.06.063.

[125] Ruela, André Luís Morais, Aline Gravinez Perissinato, Mônica Esselin de Sousa Lino, Paula Silva Mudrik, and Gislaine Ribeiro Pereira. "Evaluation of Skin Absorption of Drugs from Topical and Transdermal Formulations." *Brazilian Journal of Pharmaceutical Sciences* 52, no. 3 (2016): 527–44. https://doi.org/10.1590/s1984-82502016000300018.

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rates of drug penetration via hair follicles as compared with the intercellular pathway across the stratum corneum are directly observed, and the precipitation of drug crystals on the skin surface is visualized after the percutaneous penetration of the cosolvent excipient in the formulation. The high-speed, three-dimensional imaging capability of SRS reveals features that cannot be seen with other techniques, providing both kinetic information and mechanistic insight into the (trans)dermal drug delivery process.[126]

MALDI

Imaging techniques like mass spectrometric imaging (MSI) offer sufficient spatial resolution to generate meaningful distribution profiles of a drug molecule across a skin section. In a study reported by Bonnel et al,[127] matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI) was used to generate quantitative skin distribution profiles based on tissue extinction coefficient determinations of four different molecules in cross-sections of human skin explants after topical administration. The four drug molecules tested (roflumilast, tofacitinib, ruxolitinib, and LEO 29102) have different physicochemical properties. In addition, tofacitinib was administrated in two different formulations. The study revealed that with MALDI-MSI, it is possible to observe differences in penetration profiles for both the four drug molecules and the two formulations and thereby demonstrates its applicability as a screening tool when developing a topical drug product. Furthermore, the study revealed that the sensitivity of the MALDI-MSI techniques appears to be inversely correlated with the ability of the drug molecules to bind to the surrounding tissues, which can be estimated by their Log D values.

FLIM

In situ biodistribution and residency of a topical anti-inflammatory using fluorescence lifetime imaging microscopy (FLIM) has been described for

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[126] Saar, Brian G., L. Rodrigo Contreras-Rojas, X. Sunney Xie, and Richard H. Guy. "Imaging Drug Delivery to Skin with Stimulated Raman Scattering Microscopy." *Molecular Pharmaceutics* 8, no. 3 (June 6, 2011): 969–75. https://doi.org/10.1021/mp200122w.

[127] Bonnel, David, Raphaël Legouffe, André H. Eriksson, Rasmus W. Mortensen, Fabien Pamelard, Jonathan Stauber, and Kim T. Nielsen. "MALDI Imaging Facilitates New Topical Drug Development Process by Determining Quantitative Skin Distribution Profiles." *Analytical and Bioanalytical Chemistry* 410, no. 11 (April 2018): 2815–28. https://doi.org/10.1007/s00216-018-0964-3.

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an investigational drug being developed for the treatment of atopic dermatitis and psoriasis.[128] Two topical formulations were applied to the right and left forearms of six participants for seven consecutive days, followed by seven days of observation for residency. FLIM images were obtained daily throughout the study. Three punch biopsies from each participant for one formulation was also obtained from the treated region during the post-treatment follow-up. Cellular and subcellular features associated with different epidermal and dermal layers were visualized noninvasively, down to a depth of 200 μm. Results yielded three-dimensional maps of the compound's spatial distribution and residency over time. This fluorescence data provided a marker that was used as a monitor for day-to-day variance of drug presence and residency post application. The results suggest FLIM could be a viable alternative to skin biopsies without the usual patient discomfort and limitations, thereby enabling the direct measurement of skin distribution through longitudinal monitoring. These results are the first step in establishing the unique capabilities that multiphoton imaging could provide to patients through noninvasive drug detection.

Tracer Studies

Using ^{14}C as a tracer, measuring radioactivity provides an opportunity to characterize the pharmacokinetics of very low concentrations, such as those observed following topical application to small surface areas (e.g. for the treatment of hyperhidrosis affecting the axilla and/or palms). As reported by Dumitrescu et al,[129] the goal of a clinical study was to evaluate the pharmacokinetics of a compound (umeclidinium (UMEC)) when administered to various anatomical sites (axilla or palm) and under occluded and non-occluded conditions. The primary objectives of this study were to characterize the pharmacokinetics in the presence and absence of occlusion, and to develop a population pharmacokinetic model of UMEC following single-dose administration to the axilla or palm. The secondary objectives

[128] Alex, A., S. Frey, H. Angelene, C. D. Neitzel, J. Li, A. J. Bower, D. R. Spillman, et al. "In situ Biodistribution and Residency of a Topical Anti-Inflammatory Using Fluorescence Lifetime Imaging Microscopy." *The British Journal of Dermatology* 179, no. 6 (2018): 1342–50. https://doi.org/10.1111/bjd.16992.

[129] Pene Dumitrescu, T., L. L. Santos, S. C. Hughes, A. I. Pereira, G. C. Young, E. Hussey, P. Charlton, et al. "A Novel Method for Studying the Pharmacokinetics of [(14) C]Umeclidinium After Application to the Axilla or Palm of Healthy Male Subjects." *Clinical and Translational Science* 9, no. 4 (2016): 183–91. https://doi.org/10.1111/cts.12406.

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were to determine the amount of UMEC potentially absorbed in the skin and to characterize the safety and tolerability of topical UMEC after single-dose administration to the axilla or palm. Modeling and simulations were used to predict plasma-concentration profiles after repeated doses, and to estimate the likelihood of exceeding the systemic exposure from the inhaled UMEC therapeutic dose, allowing bridging of the systemic safety to the inhaled program. A feasibility assessment based on in-house IVPT data suggested that the established validated bioanalytical method using LC-MS/MS would provide insufficient sensitivity to quantify UMEC plasma concentrations following dermal administration. A novel translational approach using ^{14}C-labeled drug applied dermally with detection by accelerator mass spectrometry (AMS) was therefore proposed to quantify the anticipated lower plasma drug concentrations. This study evaluated the pharmacokinetics, safety, and tolerability of a single dose of [^{14}C]UMEC applied to either un-occluded axilla, occluded axilla, or occluded palm of healthy males. [^{14}C]UMEC plasma concentrations were quantified by AMS. Occlusion increased systemic exposure 3.8-fold. Simulated systemic exposure following daily doses applied to axilla was similar to the exposure from the marketed inhaled route of administration,[130] suggesting that systemic safety following dermal administration could be bridged to the inhaled program, and offering the potential for a reduced number of studies and/or patients.

Dermal Open-Flow Microperfusion (dOFM)

An additional FDA collaboration was with international researchers to evaluate a new method for monitoring the amount of a topical drug in the dermis. In a procedure called dermal open-flow microperfusion (dOFM), a thin, hollow tube is inserted under the skin surface: a portion of the tube under the skin is porous, so any drug that has been applied and absorbed through the skin's outer layer enters the flowing liquid, which is then collected for analysis.

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[130] Goyal, Navin, Misba Beerahee, Chris Kalberg, Alison Church, Sally Kilbride, and Rashmi Mehta. "Population Pharmacokinetics of Inhaled Umeclidinium and Vilanterol in Patients with Chronic Obstructive Pulmonary Disease." *Clinical Pharmacokinetics* 53, no. 7 (July 2014): 637–48. https://doi.org/10.1007/s40262-014-0143-4.

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This method was initially evaluated in a clinical study conducted by Bodenlenz et al[131] that evaluated whether dOFM could reliably measure the changing amounts of drug in the skin after topical application of a dermatological drug product. In this single-center clinical study, reference (R) or test (T) products were applied to six randomized treatment sites on the skin of 20 healthy volunteers. Two dOFM probes were inserted in each treatment site to monitor the intradermal acyclovir concentration for 36 hours. Comparative BA (of reference *vs*. reference and test *vs*. reference) was evaluated based on conventional BE criteria for pharmacokinetic endpoints (area under the curve and maximum dermal concentration) where the 90% confidence interval of the geometric mean ratio between the test and reference falls within 0.80 to 1.25. The study demonstrated that the dOFM pharmacokinetic approach could accurately and reproducibly confirm that the reference product was bioequivalent to itself at different anatomical sites. Furthermore, the dOFM approach was sufficiently sensitive to discriminate between the pharmacokinetics of the reference and test products, which were confirmed not to be bioequivalent.

In addition to acyclovir, a hydrophilic drug with little protein binding, the applicability of dOFM for other topical drug products that are moderately lipophilic and moderately or highly protein bound, such as lidocaine and prilocaine, respectively, was investigated in a pilot study in healthy volunteers conducted by Tiffner et al.[132] In this study, the ability of dOFM to characterize the cutaneous pharmacokinetic profiles for topical lidocaine and prilocaine, including dose-dependent response and formulation differences, supports the general utility of dOFM to investigate the cutaneous pharmacokinetics of lipophilic and protein bound drugs.

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[131] Bodenlenz, Manfred, Katrin I. Tiffner, Reingard Raml, Thomas Augustin, Christian Dragatin, Thomas Birngruber, Denise Schimek, et al. "Open Flow Microperfusion as a Dermal Pharmacokinetic Approach to Evaluate Topical Bioequivalence." *Clinical Pharmacokinetics* 56, no. 1 (2017): 91–98. https://doi.org/10.1007/s40262-016-0442-z.

[132] Tiffner Katrin, Thomas Birngruber, Gerd Schwagerle, et al. "Evaluation of Dermal Open Flow Microperfusion (dOFM) as a General Methodology to Assess the Bioequivalence of Hydrophobic, Protein-Bound Topical Drug Products." Poster M0930-05-033. Presented at AAPS PharmSci 360; Washington, DC; November 2018. https://www.eventscribe.net/2018/PharmSci360/fsPopup.asp?efp=UUFSQlZZVFM1OTQ2&PosterID=166379&rnd=0.7744293&mode=posterinfo.

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Prior to the conduct of the acyclovir study establishing the potential for dOFM to determine the BE of topical products, Dragatin et al[133] demonstrated the utility of dOFM for evaluating target engagement of a drug as well as pharmacokinetics in the skin by measuring the concentration of secukinumab, a monoclonal antibody effective for plaque psoriasis that selectivity targets and neutralizes IL-17A, directly in the skin of healthy volunteers and in lesional and nonlesional skin of patients with plaque psoriasis. This study was designed to assess the ability of a single 300 mg subcutaneous dose of secukinumab to neutralize IL-17A in the skin. The authors concluded that secukinumab concentrations in the skin, as measured by dOFM, were similar on Day 8 and Day 15 postdosing, lower in patients with psoriasis compared with healthy volunteers, and corresponded to secukinumab concentrations determined by suction blister and punch biopsy. The secukinumab concentrations in lesional skin were in excess of the level of IL-17A detected at baseline in the same plaques, which supported the clinical efficacy demonstrated by clinical endpoints.

An additional application of dermal microdialysis is to evaluate the effect of formulation wipe-off time on the topical bioavailability of a topically applied drug. Kuzmaetal[134] evaluated the effect of formulation removal on dermis exposure from the application of two formulations (gel and cream) of metronidazole to Yucatan minipigs. Dermis metronidazole exposure from the gel was independent of wipe-off, suggesting that drug delivery from the gel is complete within 6 hours, whereas drug delivery from the cream was slower than the gel and complete within 12 hours.

Regulatory

The EMA has issued a draft guideline on using quality and equivalence testing of topical products in lieu of therapeutic equivalence clinical

[133] Dragatin, Christian, Florine Polus, Manfred Bodenlenz, Claudio Calonder, Birgit Aigner, Katrin Irene Tiffner, Julia Katharina Mader, et al. “Secukinumab Distributes into Dermal Interstitial Fluid of Psoriasis Patients as Demonstrated by Open Flow Microperfusion.” *Experimental Dermatology* 25, no. 2 (February 2016): 157–59. https://doi.org/10.1111/exd.12863.

[134] Kuzma, Benjamin, Sharareh Senemar, and Grazia Stagni. (2018). “Effect of Formulation Wipe-off Time on Topical Bioavailability of Metronidazole Using Dermal Microdialysis.” 2018. Poster W1030-02-016. Presented at AAPS PharmSci 360; Washington, DC; November 2018. DOI: 10.13140/RG.2.2.29023.10405.

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trials.[135] Guidance is provided on models and studies that may be used to independently determine equivalence with respect to (i) quality, (ii) efficacy, and (iii) safety that, taken together, support a claim of therapeutic equivalence, when the method of administration is the same and risks of inequivalence to the patient are minimal.

Equivalence test protocols are provided for the following:

- *in vitro* release testing (IVRT)
- *in vitro* human skin permeation testing (IVPT)
- *in vivo* stratum corneum sampling (tape stripping)
- *in vivo* vasoconstriction assay for corticosteroids

In vitro and *in vivo* Correlations

Clinical doses of topical agents are selected based on *in vitro*/*in vivo*/*ex vivo* potency, preclinical IV/oral clearance parameters from PK studies and systemic and dermal toxicokinetics from repeat dose general toxicology studies. Prior to first in human studies, the systemic exposure considering the dose (which accounts for both formulation strength and application area) and dosing frequency should be predicted using allometric scaling of PK parameters from rodent and non-rodent species, although the bioavailability of the applied compound through the skin will need to be estimated, considering likely variability. Projected systemic exposure (Cmax and AUC) in humans should be used to compare to the animal toxicokinetics at the NOAEL exposures to estimate safety/exposure margins. Skin PK from *in vitro* penetration studies and from *in vivo* minipig studies should also be considered to confirm penetration and delivery to the appropriate site of action in the skin (epidermis and/or dermis) to project the desired concentration strength of the formulation needed for therapeutic benefit.

Analogous to the dissolution methods used for solid dosage forms, IVPT is the most commonly used technique to assess the potential for bioavailability and bioequivalence of topical formulations.

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[135] European Medicines Agency. Draft Guideline on Quality and Equivalence of Topical Products. CHMP/QWP/708282/2018. October 2018. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-quality-equivalence-topical-products_en.pdf.

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To examine whether *in vitro* and *ex vivo* measurements of topical drug products correlate with *in vivo* outcomes, Leal et al[136] compared *in vitro* drug release and drug penetration into porcine skin *ex vivo* with published human *in vivo* studies. Two betamethasone valerate formulations, and three marketed econazole nitrate creams were assessed. For betamethasone valerate, uptake in the stratum corneum closely matched the human data and distinguished between inequivalent formulations. Uptake of econazole nitrate mirrored the *in vivo* equivalence. However, econazole nitrate clearance from the stratum corneum did not parallel *in vivo* results, presumably due to the absence of functioning microcirculation. *In vitro* release of betamethasone did not overlap with *ex vivo* data, although a good correlation was observed for econazole nitrate. The authors concluded that "*in vitro* and *ex vivo* methods for topical bioequivalence determination can show correlation with *in vivo* outcomes. However, these surrogates have understandable limitations. A one-size-fits-all approach for topical bioequivalence evaluation may not always be successful; therefore, and the judicious use of complementary methods may prove a more effective and reliable strategy".

In conclusion, several promising options exist for evaluating the pharmacokinetics of both topically applied and systemically administered drugs. Topical drug products can be complex, and minor differences in vehicle formulations can influence topical bioavailability. A comprehensive research strategy, including physical and structural product characterization, IVRT, IVPT, and *in vivo* methods should be considered when evaluating and comparing formulations.

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[136] Leal, Leila Bastos, Sarah F. Cordery, M. Begoña Delgado-Charro, Annette L. Bunge, and Richard H. Guy. "Bioequivalence Methodologies for Topical Drug Products: *In vitro* and *Ex vivo* Studies with a Corticosteroid and an Anti-Fungal Drug." *Pharmaceutical Research* 34, no. 4 (2017): 730–37. https://doi.org/10.1007/s11095-017-2099-1.

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CHAPTER 5

PEDIATRIC CONSIDERATIONS

Pediatric patients represent a significant population for treatment of many dermatological conditions such as atopic dermatitis, acne vulgaris, molluscum contagiosum, and hyperhidrosis. Genetic disorders such as epidermolysis bullosa often demonstrate the symptoms at birth. Even for skin conditions that do not affect the pediatric population very often (e.g. psoriasis), it is a requirement to assess its pediatric impact and discuss with regulatory authorities. This mandatory process is called pediatric study plan (PSP) and pediatric investigational plan (PIP) for the US and EU, respectively.

Absorption of drugs via the skin is influenced by both physical and chemical characteristics of the drug and by the barrier properties of the skin. Skin maturation has been well described, with the potential for systemic toxicity recognized in neonates and infants resulting from percutaneous absorption of topically-applied substances such as alcohols, hexachlorophene, neomycin, and corticosteroids.[137] The direct correlation between risk and younger age is related to the higher surface-area-to-weight ratio (BSA/mass) in infants. In contrast to adults, infant skin is in a constant state of flux with changes in TEWL, hydration, lipid content, and skin acidity.[138] Skin maturation as well as the condition of the skin, such as a weakened skin barrier, and dosing practice, such as occlusion, must be considered when treating pediatric patients. High risk populations and conditions include premature infants and those with genetic skin disorders such as Netherton syndrome, ichthyosis, and inflamed skin diseases (including atopic dermatitis).

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[137] Mancini, Anthony J. "Skin." *Pediatrics* 113, no. Supplement 3 (April 1, 2004): 1114–19. https://pediatrics.aappublications.org/content/113/Supplement_3/1114.

[138] King, Alice, Swathi Balaji, and Sundeep G. Keswani. "Biology and Function of Fetal and Pediatric Skin." *Facial Plastic Surgery Clinics of North America* 21, no. 1 (February 2013): 1–6. https://doi.org/10.1016/j.fsc.2012.10.001.

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Pediatric assessment, including PSP and PIP, is now a required component of every drug marketing application to FDA (US) and EMA (EU), unless a waiver has been previously granted. Several guidelines are available for nonclinical safety evaluation that provide guidance on the timing of animal studies with respect to the development of medications for pediatric patients.[139,140] It is thought that organ systems at highest risk for drug toxicity are those that undergo significant postnatal development. Evaluation of postnatal developmental toxicity is thus a primary concern. Nonclinical juvenile toxicity studies are often required as part of the pediatric assessment; the study protocols are best devised in consultation with the regulatory authorities.[141]Factors considered in the decision to conduct juvenile studies include pediatric indication, age of the intended pediatric population, duration of treatment, toxicity of the drug in adult nonclinical species (or humans), or if target organs identified in adult nonclinical species undergo significant postnatal development. The structural and functional characteristics of many organ systems differ significantly between children and adults as a result of the growth and development that takes place during postnatal maturation. When performing nonclinical studies, the intended clinical route of administration and drug product formulation should be used, unless an alternative route of administration and dose formulation provides greater exposure or is less invasive with adequate exposure. However, it is often the case for dermal drug development that administration of the drug product results in limited to no systemic exposures; an alternative route of administration, such as oral or subcutaneous injection, is therefore necessary for evaluation of systemic toxicity in the juvenile animals.

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[139] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). S5(R3): Detection of toxicity to reproduction for human pharmaceuticals (Draft). July 2017. https://www.fda.gov/media/108894/download.

[140] European Medicines Agency. ICH guideline S11 on nonclinical safety testing in support of development of paediatric medicines (Draft). EMA/CHMP/ICH/616110/2018. September 2018. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-s11-nonclinical-safety-testing-support-development-paediatric-medicines-step-2b-draft_.pdf.

[141] Barrow, Paul C., and Georg Schmitt. "Juvenile Nonclinical Safety Studies in Support of Pediatric Drug Development." In *Drug Safety Evaluation: Methods and Protocols*, edited by Jean-Charles Gautier, 25–67. Methods in Molecular Biology. New York, NY: Springer New York, 2017. https://doi.org/10.1007/978-1-4939-7172-5_2.

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Several factors should be considered in the design of juvenile safety studies. Most importantly, the maturation of human and animal organ systems across species is not uniform: the relative maturity at birth and rate of postnatal development can be quite different. Understanding the age-dependent development of organ systems by species can be attained through literature reviews and guidance documents. In the case of skin, general considerations in development include critical neonatal function (barrier, water and thermoregulatory, conductance, sensation) and progressive acidification, local microbiome, and immune function.

When selecting an appropriate species, it is important to have an understanding of the ontogeny of the pharmacological or toxicological target in animals compared with the intended pediatric population; the relative stage of toxicity target organ development in the juvenile animal; the similarity of absorption, distribution, metabolism, and excretion characteristics; and the practical feasibility of conducting the study in the selected species. In principle, a single species is considered sufficient for a juvenile animal study, and the rat is generally selected as acceptable. In the case of the rat, the epidermis thickens in the first 2 weeks of age, hair develops postnatally and structurally resembles adult by postnatal day 21, but is not fully developed until adulthood at postnatal day 70. The closest species to humans with respect to postnatal skin development is the minipig, where the skin is structurally and functionally fully mature by adulthood, which is by approximately 6 months of age in the minipig. The minipig provides the best model for dermal studies, given their many similar development milestones to humans: a relatively large size at birth; a large litter size allows for balanced sex distribution and allocation of piglets to different endpoints; and a short development timeline at 6 to 9 months. However, disadvantages include less well-established historical control data, the larger body size requires larger amounts of drug product than rodents, and IV and oral gavage administration can be challenging in very young piglets.

Preliminary dose-range finding studies should be conducted to evaluate tolerability and toxicokinetics in a small group size of juvenile animals at the relevant age prior to conducting larger definitive studies. The age of dosing initiation in the animals should developmentally correspond to the youngest age of the intended pediatric population, which will depend on comparison of the animal to human in development of the organ systems of toxicological concern. Determining the dosing duration in juvenile animal studies can be challenging, given that the dosing period can be defined by the clinical dosing duration, pediatric age stages, and stages of organ

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development. A longer dosing period in animals is usually most useful to address concerns in organ systems that develop late, and to capture the developmental age range of the intended pediatric population (2 to 12 years). In general, an off-treatment period should also be included to understand reversibility of a specific drug-related effect. An adequate number of animals (males and females) to evaluate endpoints should be included, and combining assessments of endpoints in the same animals can be effective in reducing the number of animals required. Core endpoints for evaluation should include mortality, clinical observations, growth, food consumption, sexual development, clinical pathology, anatomic pathology, and toxicokinetics. Additional endpoints include skeletal examinations, ophthalmologic examinations, central nervous system assessments, reproductive assessments, and immunologic assessments.[142]

In addition to including pediatric patients in clinical trials, regulatory agencies require submission of pediatric development plans under the Pediatric Research Equity Act (PREA),[143] which gives the FDA authority to require pediatric studies for certain drugs and age groups,[144] and the Paediatric Committee (PDCO) for the European Medicines Agency (EMA). It is important to submit an initial pediatric study plan (iPSP)[145]in the US after phase 2, and to submit a pediatric investigation plan (PIP),[146,147]in the

[142] Remick, Amera K., Natasha R. Catlin, Erin M. Quist, Thomas J. Steinbach, and Darlene Dixon. "Juvenile Toxicology: Relevance and Challenges for Toxicologists and Pathologists." *Toxicologic Pathology* 43, no. 8 (December 2015): 1166–71. https://doi.org/10.1177/0192623315595883.

[143] United States Government. "Pediatric Research Equity Act." Public Law 108-155, 117 Stat. 1936–43 – Dec 3, 2003. Accessed October 2019. https://www.govinfo.gov/content/pkg/STATUTE-117/pdf/STATUTE-117-Pg1936.pdf.

[144] Food and Drug Administration. Pediatric Research Equity Act (PREA). November 2019. https://www.fda.gov/drugs/development-resources/pediatric-research-equity-act-prea.

[145] Food and Drug Administration. *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans*. Guidance for Industry (Draft). March 2016. https://www.fda.gov/media/86340/download.

[146] European Medicines Agency. "Paediatric Investigation Plans." https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans.

[147] European Medicines Agency. "Paediatric investigation plans: Templates, forms and submission dates." https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans/paediatric-investigation-plans-templates-forms-submission-dates.

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EU after adult pharmacokinetic studies are complete: a delay in submission and agreement on these plans could delay the marketing authorization of the drug in adults. In many cases, a waiver or deferral for pediatric clinical studies may be requested and granted for specific age groups. If the drug has been granted orphan designation for the proposed indication, an iPSP is not required in the US, but a PIP is still required in the EU. In some situations, sponsors may consider requesting a pediatric exclusivity provision in return for conducting pediatric studies under the US Best Pharmaceuticals for Children Act (BPCA).[148] The BPCA is an incentive program. The FDA sends a Written Request to the sponsor/drug company to perform one or more pediatric clinical studies; the sponsor has the option to accept or decline the request because performing BPCA clinical trials is voluntary.[149] If the sponsor accepts the request, they conduct the pediatric clinical trials and submit results to the FDA. If the studies are completed as outlined in the request, the FDA will grant the sponsor a reward of an additional 6 months of marketing exclusivity for the compound that was studied. After pediatric studies are completed, the agency reviews the new clinical data and updates the product labeling to inform healthcare providers regarding the safe and effective use of the drug in the pediatric population. The BPCA incentive can be used in conjunction with the PREA requirements to maximize pediatric drug development.

In generating the iPSP and PIP, an overview of the disease condition in the pediatric population is required. This includes descriptions of the pathophysiology of the disease, methods of diagnosis, currently available treatments in the pediatric population, including neonates, and data on the incidence and prevalence of the condition in the pediatric population. Additionally, an understanding of the key differences between the disease in adults and pediatric populations should be provided. Extrapolation of effectiveness may be appropriate from adults to pediatric age groups, and from one pediatric age group to another, although an understanding of exposure-response is critical. Modeling and simulations are used to support extrapolation as well as the dose rationale for each age group. While a

[148] United States Government. "Best Pharmaceuticals for Children Act." Public Law 107-109 – Jan 4, 2002. Accessed October 2019. https://www.govinfo.gov/content/pkg/PLAW-107publ109/pdf/PLAW-107publ109.pdf.

[149] Avant, Debbie, Gerold T. Wharton, and Dianne Murphy. "Characteristics and Changes of Pediatric Therapeutic Trials under the Best Pharmaceuticals for Children Act." *The Journal of Pediatrics* 192 (January 1, 2018): 8–12. https://doi.org/10.1016/j.jpeds.2017.08.048.

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dedicated pharmacokinetic study may not be required in each age group, population pharmacokinetic studies and analyses are important to confirm the proposed dosing.

It is important to plan for clinical studies in pediatric age groups early in the development program of a new product as toxicology studies will be required prior to enrolling younger patients, and if not timed appropriately may result in delays to the overall program. An understanding of the overall absorption, distribution, metabolism and elimination is also critical to understanding whether the systemic exposure is likely to be age-dependent. If no clinical and/or exposure data are available in younger patients, a sufficient understanding of the risk/benefit in adults should be established initially, with staggered exposure in younger age groups. Studies are typically conducted in adolescent patients followed by 6- to 11-year-olds, then 2- to 5-year-olds, and finally in under 2-year-olds, as needed. Pharmacokinetic studies and/or pharmacokinetic/pharmacodynamic studies may be sufficient for providing dosing recommendations in the product label. MUsTs are also likely to be required for each age group. If clinical efficacy and safety studies are planned, pharmacokinetic sampling may be included to address the exposure-response, particularly to address systemic safety. As opportunities for blood sampling may be limited in younger patients (both from the blood volume required as well as the willingness for multiple venipunctures), sparse sampling strategies, based on prior understanding of the pharmacokinetic profile in older patients are more easily justified. Sparse samples collected from all patients or more intensive sampling from a subset of patients can be pooled together to evaluate population pharmacokinetic parameters and covariates, such as age, body weight, BSA, severity of disease, TEWL, and sex. Physiologically-based pharmacokinetics (PBPK) can be used to bridge the gaps in the pediatric age groups as a PBPK model has no limitation in evaluating levels below the limit of quantification.

As with adults, it is critical to collect complete dosing and sampling information in clinical trials from the patient or caregiver with accurate recording in the case report form for the study. Collection of other relevant information, such as skin condition (e.g. presence of erythema, TEWL) should also be encouraged. As doses are most likely to be applied by the caregiver (such as parent or guardian) for a pediatric patient, the application method should be well described with consideration for the surface area of application, the amount that is to be applied per designated surface area, the sites of application (e.g. face *vs.* other body areas), how to rub the product

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onto the skin, whether the application site is to be occluded (such as with a diaper), and how long to wait before the application site may be washed.

A recent example describes learnings from a study of crisaborole ointment. Three pediatric-age cohorts (12 to 17 years, 6 to 11 years, and 2 to 5 years) with atopic dermatitis participated in a phase 1b, open-label, maximum usage trial.[150]The study drug (3 mg/cm^2) was applied for 28 days, with blood samples for pharmacokinetic analysis collected on Day 1 and Day 8 at 3, 12, and 24 hours and prior to dosing on Days 2, 7, 8, and 9 for analysis of crisaborole and metabolites. Crisaborole was rapidly absorbed, with limited systemic exposure between Days 1 and 8. Of note, there was considerable similarity in pharmacokinetic profiles, with no significant between-group differences in age-based cohorts; the authors concluded that the observed plasma levels were consistent with those previously reported in adults, with adjustments for the affected BSA. The authors also concluded that the study findings supported favorable safety and tolerability in children as young as 2 years of age. These data supported phase 2 and phase 3 clinical development in patients 2 years of age and older. The applicant was granted a waiver for studies in children 0 to <3 months of age on the basis that studies are impractical because the diagnosis of atopic dermatitis is uncommon and often unreliable before the age of 8 months.[151] A deferral for children 3 months to <2 years of age was granted, and a study in children aged 3–24 months with mild to moderate atopic dermatitis has now been completed.[152]

Additional analyses and interpretation of the systemic exposures from crisaborole ointment have been reported, and emphasize how comprehensive analysis of all available pharmacokinetic data, including data from healthy

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[150] Zane, Lee T., Leon Kircik, Robert Call, Eduardo Tschen, Zoe Diana Draelos, Sanjay Chanda, Merrie Van Syoc, and Adelaide A. Hebert. "Crisaborole Topical Ointment, 2% in Patients Ages 2 to 17 Years with Atopic Dermatitis: A Phase 1b, Open-Label, Maximal-Use Systemic Exposure Study." *Pediatric Dermatology* 33, no. 4 (July 2016): 380–87. https://doi.org/10.1111/pde.12872.

[151] Food and Drug Administration. Center for Drug Evaluation and Research. *Application Number 207695Orig1s000 Summary Review*. 2016. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/207695Orig1s000SumR.pdf.

[152] Pfizer Inc. "A Study of Crisaborole Ointment 2% in Children Aged 3-24 Months with Mild to Moderate Atopic Dermatitis." ClinicalTrials.Gov. Accessed December 2019. https://clinicaltrials.gov/ct2/show/results/NCT03356977.

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volunteers and from atopic dermatitis patients can be utilized.[153]Linear slope-intercept models with weight included as a covariate (allometric power function) were used to describe the relationship between pharmacokinetic parameters and the ointment dose. Effects of other covariates, such as disease status/severity, race, and sex, on the slope were tested. Non-linear regression analyses were also conducted. Based on these analyses, at a similar percent BSA-treated, exposures (bioavailability) were demonstrated to be approximately the same for 2 years and above, and the exposures in children at maximum possible doses are unlikely to exceed exposures at the maximum possible dose in adults. However, there should be caution in generalization of results, as bioavailability could be higher or lower in pediatric patients if there is greater disease severity, skin barrier impairment, a higher affected BSA, or alterations of systemic clearance.

Study designs of the MUsT for different indications may vary, but the example above, evaluating maximum possible dose, should be useful. Although the MUsT is a US requirement for topical drug development, the EU is also interested in collecting and reviewing pharmacokinetic data. A stand-alone pharmacokinetic study for pediatric population may not be necessary for EU and Japan, but it would be necessary to conduct sparse pharmacokinetic sampling and have population pharmacokinetic analysis as a part of the safety assessments and justification of the pediatric dose. Sparse sampling in pediatric patients in phase 2 studies may be sufficient and useful, and may provide justification for not collecting blood samples in pediatric phase 3 studies. Having frequent blood collections in the pediatric population may often delay recruitment of clinical trials, and this is an operational risk for phase 3 studies that are always exposed to intense pressure of timelines.

When and how to include pediatric populations (and each age group) in clinical studies is not only a medical and scientific decision, but also an operational and business decision. Unless safety is an issue, the sponsor should be prepared to include all pediatric population subsets in the standard development plan. It is mandatory to prepare a PSP and/or PIP for new drug products; medical justifications are required to defer (delay) the start of

[153] Purohit VK. “Analysis and Interpretation of Systemic Exposures from Topical Agents: Learnings from Crisaborole Ointment.” Presented at Topical Drug Development: Evolution of Science and Regulatory Policy, Baltimore, Maryland, July 2019.
https://www.pharmacy.umaryland.edu/media/SOP/wwwpharmacyumarylandedu/centers/cersievents/topical/purohit-presentation_072919.pdf.

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pediatric studies or to request a waiver for conducting studies in specific pediatric age groups. Expectation of operational difficulties is not sufficient justification for a waiver; the sponsor should therefore design a study that is feasible to recruit and execute and obtain agreement with the regulatory agencies. These types of studies often become postmarketing commitment studies, and the sponsor must fulfill the commitment. If challenges completing the study are encountered, the sponsor needs to discuss the issues with the relevant regulatory agency, propose a new plan, and obtain agreement with the modified plan.

In conclusion, pediatric studies for all age groups should be planned early in the drug development process. Robust planning, including regulatory interactions, is paramount to meeting the needs of pediatric patients impacted by dermatological conditions.

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CHAPTER 6

DISEASE-SPECIFIC LATE-STAGE CLINICAL DEVELOPMENT

In this chapter, the authors would like to share their disease-specific clinical development experience. The intent is to provide examples and points to consider for several different common and rare dermatologic conditions, rather than to present a step-by-step manual for drug approval.

Drug development is an iterative learning process for both the sponsor (the pharmaceutical industry) and the regulatory authorities. There are overarching laws and statutes that must be followed in research, but most of the details are contained within guidance documents published by the regulatory authorities to provide recommendations on specific topics based on experience to date. In the US, the guidance documents clearly state that they represent the current thinking of the FDA, and that the recommendations are not binding. As the industry evolves and new information and best practices become available, the guidances will be updated as necessary. Working closely with regulatory colleagues/advisers to keep up-to-date on current processes is important. Since regulatory processes may progress more slowly than science, working closely with the agencies before implementing any new study design features is highly recommended. Even if a new assessment technique or endpoint has not been used for another product, there is always an opportunity to be first!

Psoriasis

Psoriasis is the flagship of immunoinflammatory skin indications from a drug development perspective. Psoriasis was one of the first dermatological indications for which biologics were introduced, and they modernized the dermatology treatment landscape. Since then, dermatological drug development has attracted many companies with immunoinflammatory or immuno-oncology candidates in their pipeline; however, psoriasis is not the initial indication studied. For example, etanercept (Enbrel®) in the US was approved for rheumatoid arthritis (RA) in 1998, followed by

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polyarticular juvenile idiopathic arthritis in 1999, psoriatic arthritis (PsA) in 2002, ankylosing spondylitis in 2003, plaque psoriasis in 2004, and pediatric plaque psoriasis in 2016. Infliximab (Remicade®) was first approved for Crohn's disease in 1998, followed by RA in 1999, ankylosing spondylitis in 2004, PsA in 2005, ulcerative colitis in 2005, pediatric Crohn's disease in 2006, plaque psoriasis in 2006, and pediatric ulcerative colitis in 2011. Another example is adalimumab (Humira®). Approval for RA was initially granted in 2002, followed by PsA in 2005, ankylosing spondylitis in 2006, Crohn's disease in 2007, plaque psoriasis in 2008, juvenile idiopathic arthritis in 2008, ulcerative colitis in 2012, pediatric Crohn's disease in 2014, hidradenitis suppurativa in 2015, and non-infectious uveitis in 2016. Humira® also added fingernail psoriasis data in the prescribing information in 2017.

The lengthy development history of tumor necrosis factor (TNF) inhibitors can tell us a lot of interesting stories. Major pharmaceutical companies were initially not so keen to develop drugs for psoriasis. Development for PsA preceded psoriasis, likely due to the similarity of diseases and endpoints between RA and PsA. Pharmaceutical companies vigorously manage the lifecycle of their assets; when there are multiple indications to explore, the company tries to maximize the efficiency of development. For example, there are opportunities to reduce redundancy in toxicological studies in animals and to reduce the number of phase 1 studies in humans; however, dose selection for the target indication is not an easy task. If several indications are targeted with the drug product, psoriasis treatment may require a higher dosage than other indications. For example, tofacitinib (Xeljanz®), one of the Janus kinase (JAK) inhibitors, was approved for RA and PsA but it was not approved for psoriasis even though efficacy was demonstrated in the phase 3 psoriasis studies. The phase 3 studies showed a more favorable efficacy with 10 mg twice daily treatment than with 5 mg twice daily treatment. In RA and PsA studies, both 5 mg and 10 mg demonstrated comparable efficacy, and 5 mg twice daily was the approved dosing regimen. From a safety perspective, 5 mg was more favorable in both indications.[154] It is assumed that only 5 mg twice daily was approved based on the risk-benefit ratio. From a safety perspective, it was probably difficult to justify 10 mg twice-daily treatment to maximize the efficacy for psoriasis, which may be viewed as a less serious condition

[154] Berekmeri, Anna, Farrouq Mahmood, Miriam Wittmann, and Philip Helliwell. "Tofacitinib for the Treatment of Psoriasis and Psoriatic Arthritis." *Expert Review of Clinical Immunology* 14, no. 9 (2018): 719–30. https://doi.org/10.1080/1744666X.2018.1512404.

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than RA or PsA, but 10 mg twice daily was approved for ulcerative colitis. From this observation, inflammatory skin diseases such as psoriasis may require a higher dosage to demonstrate efficacy than some other inflammatory conditions such as RA and PsA.

In this author's opinion, after monoclonal antibodies targeting the interleukin (IL)-17 pathway (e.g. secukinumab) were introduced into the market, an indication targeting moderate to severe plaque psoriasis became congested. The efficacy of these agents already achieved close to 100% improvement on the psoriasis area severity index (PASI) and clear or almost clear skin. The next movement is toward niche areas like nail psoriasis and genital psoriasis that significantly affect daily activities and quality of life, although the affected surface area may not be large enough to categorize overall severity as moderate or severe. This strategic move has already been observed with Humira® adding fingernail psoriasis data in the prescribing information. It would be interesting to see how the recently approved IL-23 monoclonal antibody risankizumab (Skyrizi™) competes with IL-17 monoclonal antibodies in the market. The efficacy level was even greater than IL-17 monoclonal antibodies, with 40% to 50% of patients achieving 100% improvement from baseline (PASI100), which is complete clearance of lesions.

While biologics for psoriasis introduced modernized dermatology clinical development, selections of the ideal efficacy endpoints for clinical trials were scrutinized. It seems to have been settled to some extent, but there are still ongoing discussions and debates. The two major efficacy endpoints used in clinical trials are the PASI and the Physician Global Assessment (PGA) (also referred to as the Investigator Global Assessment [IGA]). PASI is a composite scoring system that includes both the severity and BSA affected: the highest score is 72. PGA is a static assessment of disease severity on a 5-point scale.

The primary endpoint to satisfy the FDA has been PGA, with a score of 0 (clear) or 1 (almost clear skin) and at least a 2-grade reduction from baseline PGA score. A 2-grade reduction is considered by the FDA to reflect a clinically meaningful change that physicians can recognize on most occasions. The idea behind this is that this is how physicians evaluate the disease in an actual clinical setting. In the clinic, physicians use dynamic assessments to monitor treatment efficacy. At each visit, they see the patient's current condition and they also refer back to the previous condition. However, for clinical trials, it is a requirement to use static assessments to assess the condition at a specific time point without referring

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to the previous condition. It is critical to standardize the description of each grade because PGA=2 (mild) may not be interpreted the same way by every evaluator. The development team often creates a training program for evaluators and raters to have the same standards using many descriptions, images, and photos; a certificate is issued when the rater passes an exam. The FDA once asked the sponsor what efforts were made to educate investigators and standardize the assessment. The online training and the certification process were accepted for that purpose.

While PGA is a requirement for the FDA, PASI has been better received by the European Medicines Agency (EMA) and Japanese Pharmaceuticals and Medical Devices Agency (PMDA). These regulators acknowledge the usefulness of PGA, but they prefer PASI for the primary endpoint in clinical trials, particularly for moderate to severe psoriasis. The psoriasis drug development guideline issued by EMA in 2004[155] is still current, and states that the PASI score has been the most frequently used primary endpoint in therapeutic confirmatory trials both for topical and systemic agents. However, PASI is not alone sufficient to evaluate psoriasis severity at baseline and on treatment and the use of two endpoints to assess efficacy is strongly recommended: PASI plus a validated, standardized global score (e.g. PGA).

Compared with PGA, PASI is regarded as more objective, but rater training is still necessary to increase data quality. To satisfy regulatory requirements across geographic regions, pharmaceutical companies who conduct global drug development programs often design clinical trials to have co-primary outcome measures using both PGA and PASI. In recent drug development for moderate to severe psoriasis, using co-primary endpoints seems to have become routine: a proportion of patients demonstrating PGA=0 or 1, and at least a 2-grade reduction from baseline (referred to as PGA success) and the proportion of patients demonstrating 75%, 90%, or 100% reduction from baseline PASI score (referred to as PASI75, PASI90, or PASI100, respectively). It is impressive to see the PASI trend shifting from PASI50 and PASI75 to PASI90 and PASI100 after the introduction of biologics and increased efficacy. Although PASI seems like a more objective rating system than PGA, it is not perfect when

[155] European Medicines Agency. Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis. CHMP/EWP/2454/02 corr. November 2004. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-indicated-treatment-psoriasis_en.pdf.

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developing drugs for mild to moderate psoriasis. PASI has poor sensitivity to change for relatively small areas of involvement, which is indicative of mild disease.[156]

Another important endpoint to consider is the change from baseline in the percentage of BSA affected by psoriasis. With a variety of safe treatment options for psoriasis, the medical board of the National Psoriasis Foundation developed a guideline to introduce the concept of "treat to target".[157] The medical board used the Delphi process for consensus of the target treatment. The Delphi Panel methodology, a scientific method for achieved expert consensus, represents a structured process used to collect knowledge by defining a problem, developing questions for experts to resolve, selecting a panel of experts including academics and clinicians, employing open-ended questionnaires, performing controlled assessment and feedback including qualitative and quantitative analysis, and follow-up (reassessment) using a series of surveys until an accord is established and summarized.[158]The target response after 3 months of treatment was an affected BSA of 1% or less, and it was also a target during the maintenance treatment. Drug developers must be *au fait* with the trends in treatment guidance as they will be used in clinical practice. Treating physicians use these assessments rather than regulatory endpoints to measure treatment success in a real-world setting. Including these endpoints in the design of late-phase clinical trials and publishing the results may add value to discussions with payers and clinicians.

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[156] Feldman, S. R., and G. G. Krueger. "Psoriasis Assessment Tools in Clinical Trials." *Annals of the Rheumatic Diseases* 64 Suppl 2 (March 2005): ii65-68; discussion ii69-73. https://doi.org/10.1136/ard.2004.031237.

[157] Armstrong, April W., Michael P. Siegel, Jerry Bagel, Erin E. Boh, Megan Buell, Kevin D. Cooper, Kristina Callis Duffin, et al. "From the Medical Board of the National Psoriasis Foundation: Treatment Targets for Plaque Psoriasis." *Journal of the American Academy of Dermatology* 76, no. 2 (February 2017): 290–98. https://doi.org/10.1016/j.jaad.2016.10.017.

[158] Hohmann, Erik, Jefferson C. Brand, Michael J. Rossi, and James H. Lubowitz. "Expert Opinion Is Necessary: Delphi Panel Methodology Facilitates a Scientific Approach to Consensus." Arthroscopy: The Journal of Arthroscopic & Related Surgery 34, no. 2 (2018): 349–51. https://doi.org/10.1016/j.arthro.2017.11.022.

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In 2016, the FDA conducted a public meeting on Patient-Focused Drug Development for Psoriasis.[159] Drug developers must be aware that obtaining patient views on efficacy is gaining popularity and may be beneficial when negotiating with payers. Further, the use of validated patient-reported outcomes (PROs) in the drug development process make it possible to include the information on the label, provided agreement with the FDA and other regulatory agencies is achieved. Another outcome from the public meeting was that it became clear to the FDA that treatment for pediatric psoriasis is a significant unmet medical need. The FDA used to tell pharmaceutical companies that it was necessary to gain 5 or more years of experience in adults prior to studying biologics in pediatric patients, but timely implementation of pediatric study plans has now become mandatory.

Although systemic treatment options for psoriasis have become abundant, topical treatment options are still limited. Topical treatment is especially important for patients with mild to moderate psoriasis and for some psoriasis phenotypes that affect a limited BSA. In addition, topical treatment is often a more favorable option for pediatric patients.

Many developments have been conducted and are ongoing in the TNF inhibitor's biosimilar area. A biosimilar is a biologic that is "similar" to another biologic medicine (known as a reference product), which is already licensed by regulatory authorities. Biosimilars are highly similar to the reference product in terms of safety, purity, and potency, but may have minor differences in clinically inactive components. In approving biosimilars, the Agencies may require that manufacturers conduct a clinical study (or studies) sufficient to establish safety, purity, or potency.

As mentioned, there are many psoriasis drugs available. The table below covers drugs approved in the US or EU between 2000 and January 2020, excluding biosimilars and TNF inhibitors (because they were extensively discussed above). Relatively new topical combination drugs are included in the table.

[159] Food and Drug Administration. *Public Meeting on Patient-Focused Drug Development for Psoriasis*. March 2018. https://www.fda.gov/industry/prescription-drug-user-fee-amendments/public-meeting-patient-focused-drug-development-psoriasis.

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Table 6-1: Recently Approved Drugs for Psoriasis

Molecule Name	Brand Name	Mechanism of Action (biologics only)	Route of Administration
Ustekinumab	Stelara	IL-12, IL-23 inhibitor	Subcutaneous
Ixekizumab	Taltz	IL-17 inhibitor	Subcutaneous
Secukinumab	Cosentyx	IL-17 inhibitor	Subcutaneous
Brodalumab	Siliq/Kyntheum/ Lumicef	IL-17 inhibitor	Subcutaneous
Guselkumab	Tremfya	IL-23 inhibitor	Subcutaneous
Tildrakizumab	Ilumya/Ilumetri	IL-23 inhibitor	Subcutaneous
Risankizumab	Skyrizi	IL-23 inhibitor	Subcutaneous
Methotrexate	Rasuvo / Otrexup		Subcutaneous
Apremilast	Otezla		Oral
Dimethyl fumarate*	Skilarence		Oral
Calcipotriene/ betamethasone dipropionate	Enstilar		Topical (Foam)
Calcipotriene/ betamethasone dipropionate	Taclonex		Topical (Ointment)
Halobetasol propionate/ tazarotene	Duobrii		Topical (Lotion)

* Not approved in the United States as of February 2020.

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Atopic Dermatitis

Atopic dermatitis also falls into the immunoinflammatory skin disease category and development pathways seem to have followed psoriasis. Similarities between the two conditions led some companies to investigate TNF inhibitors for atopic dermatitis, expecting a similar response to psoriasis; however, TNF inhibitors showed little utility for the treatment of atopic dermatitis.[160]Apremilast (Otezla®), a systemic phosphodiesterase 4 (PDE4) inhibitor, was also approved for psoriasis, but results were underwhelming for atopic dermatitis.[161] On the contrary, crisaborole (Eucrisa®), a topical PDE4 inhibitor, was approved for atopic dermatitis, but was not pursued for psoriasis.[162] Atopic dermatitis is clearly a different disease than psoriasis, but it is interesting to compare these diseases from the drug development viewpoint.

Atopic dermatitis primarily affects children. Therefore, it is critical to prepare and submit pediatric plans to regulatory agencies (initial Pediatric Study Plan (PSP) to the FDA and a Pediatric Investigation Plan (PIP) to the EMA) early in the development process because reaching an agreement may take a year or longer. The FDA Dermatologic and Ophthalmic Drugs Advisory Committee discussed the timing of pediatric drug development and created a guidance document in 2015.[163] Clinical studies of topical drug products have generally included pediatric patients before the initial marketing approval and the guidance added recommendations on timing for inclusion of pediatric patients in studies for systemic drugs. Factors to consider before enrollment of each pediatric age subgroup include results of juvenile toxicology studies and pharmacokinetic studies in adults and

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[160] Guttman-Yassky, Emma, James G. Krueger, and Mark G. Lebwohl. "Systemic Immune Mechanisms in Atopic Dermatitis and Psoriasis with Implications for Treatment." *Experimental Dermatology* 27, no. 4 (2018): 409–17. https://doi.org/10.1111/exd.13336.

[161] Volf, Eva M., Shiu-Chung Au, Nicole Dumont, Pamela Scheinman, and Alice B. Gottlieb. "A Phase 2, Open-Label, Investigator-Initiated Study to Evaluate the Safety and Efficacy of Apremilast in Subjects with Recalcitrant Allergic Contact or Atopic Dermatitis." *Journal of Drugs in Dermatology: JDD* 11, no. 3 (March 2012): 341–46.

[162] Moustafa, Farah, and Steven R. Feldman. "A Review of Phosphodiesterase-Inhibition and the Potential Role for Phosphodiesterase 4-Inhibitors in Clinical Dermatology." *Dermatology Online Journal* 20, no. 5 (May 16, 2014): 22608.

[163] Food and Drug Administration. *Atopic Dermatitis: Timing of Pediatric Studies During Development of Systemic Drugs*. Guidance for Industry. October 2018. https://www.fda.gov/media/117570/download.

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whether the formulation is appropriate for pediatric patients or whether a new formulation will be necessary.

Assuming safety is not an issue, enrolling infants as young as 3 months of age may be reasonable, but the pediatric plans must first be discussed and agreement reached with the FDA, EMA, and PMDA. Each agency may have different recommendations and requirements. For topical drug development, adolescents 12 years and older may be included in studies with adults since there is no difference in the skin maturation stage. Children between 2 and 12 years old may be studied after nonclinical juvenile toxicology study results support the safety of the drug product for the relevant age group and treatment duration. Take a conservative approach when deciding the youngest age group to enroll in pediatric studies until pharmacokinetic studies clarify the relationship between systemic exposure and safety parameters. Post-marketing commitment studies or studies during the review period may be allowed for the younger age groups. Open-label studies using only active treatment(s) may be permitted for very young patients. An open-label study design often reduces operational burdens and improves enrollment; it is therefore worth considering for pediatric studies, but negotiation with regulatory agencies will be necessary. There are many other factors, including operational aspects, to consider when deciding how to divide or combine pediatric studies based on age ranges. Accommodating all feedback from different regulatory agencies into a single protocol design may be time consuming and add complexity to the design, while conducting separate studies to satisfy each agency is costly. The time required to balance these factors and achieve internal (corporate) and external (regulatory agencies and investigators) agreement should be considered in the overall timelines.

Emollients are the basic, indispensable skincare for atopic dermatitis. The vehicles used for topical drug products also have an emollient effect. Historically, this has resulted in a high placebo (vehicle) effect in atopic dermatitis, which may reduce the treatment difference observed between the active and vehicle treatment groups in clinical studies. When designing efficacy studies for topical drug products using different application frequencies, you may want to also have multiple vehicle (placebo) groups to match with each of the different application frequencies (e.g. once a day, twice a day, once a week).

The clinical endpoints used in atopic dermatitis studies mirror the endpoints used for psoriasis. The investigator global assessment (IGA) and eczema area severity index (EASI) have been the gold standards for primary

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efficacy endpoints. As discussed for psoriasis drug development, the FDA prefers IGA success as the primary endpoint (using defined as a score of 0 (clear) or 1 (almost clear skin) and at least a 2-grade improvement from baseline) in phase 3 studies, while the EMA and PMDA prefer the EASI (using responder analysis such as EASI50 or EASI75), particularly in studies for moderate to severe atopic dermatitis, which is usually treated with oral or biologic therapies.

The specific EASI endpoint may vary depending on the expected efficacy of the drug. For example, the endpoint may be EASI50, EASI75, or EASI90 for the phase 3 studies. After the approval of dupilumab (Dupixent®; an IL-13 and IL-14 inhibitor), the EASI75 is gaining popularity as the primary endpoint for systemic treatment studies. EASI75 represents the percentage of patients who achieve at least 75% improvement (i.e. reduction) from baseline EASI score (similar to the concept of PASI75, which is used for psoriasis studies). For a phase 2 study, it is worth considering use of percent change from baseline in EASI score because it gives more granular view of the efficacy trends than a responder analysis such as EASI75. IGA success should also be assessed in phase 2 in order to properly design phase 3 studies. It is useful to understand that the responder analyses using IGA and EASI should be well correlated if the study appropriately manages variability by proper training of the investigators and raters. The hurdle to achieve EASI75 is little lower than that of IGA success,[164] while the hurdle for EASI90 is most likely higher than IGA success. Assessing these endpoints thoroughly is key to having successful phase 3 studies. IGA may be more suitable for studies evaluating mild to moderate atopic dermatitis because the EASI is less sensitive to change when %BSA is relatively small. As mentioned in the overall process of drug development, there was an industry-wide effort involving clinical experts in dermatology to standardize the endpoint using validated IGA (vIGA-AD™). Further efforts have focused on standardized training for IGA, EASI, and BSA measurement. These training modules are available by accessing the International Eczema Council's website.[165]

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[164] Simpson, Eric L., Bolanle Akinlade, and Marius Ardeleanu. "Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis." *The New England Journal of Medicine* 376, no. 11 (16 2017): 1090–91. https://doi.org/10.1056/NEJMc1700366.

[165] International Eczema Council. "New Tools for Atopic Dermatitis Clinical Investigators." Accessed October 2019. https://www.eczemacouncil.org/for-medical-professionals/educational-modules/.

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Different geographical regions have different practices and policies with respect to study design, which may be reflected by differences in regulatory feedback. The EMA usually requests controlled studies with a comparison between the investigational drug product and standard of care (i.e. an active comparator when available) for the target disease. Identifying which active comparator to use and justifying the selection will involve thorough research and negotiation because this selection will impact the difference in treatment effects observed and the types of analyses conducted in the clinical study, and will be a factor in determining the post-approval pricing and reimbursement. For example, a phase 3 study using an active comparator with similar efficacy (e.g. demonstrating at least noninferiority) would likely result in competitive pricing. The cost of obtaining the active comparator from the manufacturer or pharmacy for use in the clinical trials is often surprisingly high. Topical drugs will have a different formulation than the active comparator, making double-blind studies more challenging. To reduce bias, regulatory agencies may suggest developing a vehicle (placebo) that sufficiently resembles the active comparator to permit blinding the study. If the active comparator is a competitor company's product, such a request takes a lot of time to be fulfilled and costly, which may make the study impossible. Clinical trial costs for topical drug development can escalate with implementation of these scenarios, bringing the cost similar to that of a systemic drug.

Topical corticosteroids are the standard of care for treatment of atopic dermatitis. Topical calcineurin inhibitors are also often used, but are not approved for children less than 2 years of age. The use of these agents is likely to remain the standard of care, even with new nonsteroidal treatments (such as crisaborole) coming to market. The primary factors in product selection are efficacy and safety, but price is a significant factor in dominating the market. Potent topical corticosteroids are very effective for short term use, but are not safe to use for extended periods. Topical corticosteroids are frequently used to control flares; however, improper and excessive use of topical corticosteroids and the resulting side-effects drew medical and social attention and created a steroid phobia. Topical steroids create many other hurdles in the development programs for atopic dermatitis. If topical corticosteroids are used as background therapy for systemic treatment for atopic dermatitis, do not discount the impact of the topical corticosteroids. For dose finding studies, background treatment with topical corticosteroids may affect study outcomes significantly and make interpretation difficult. Depending on the potency, topical steroids may mask the true efficacy of the systemic drug. The difference between active treatment and a placebo may become small as the placebo group also has

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topical corticosteroids as the background therapy, run-in period treatment, or as rescue therapy, which may demonstrate unexpectedly high efficacy.[166]

When conducting an active comparator study using topical corticosteroids, it is necessary to pay extra attentions to the study design. If topical corticosteroids are used as the comparator, what would be the impact on business? And how about the medical community? The medical community always wants to have more supportive data, particularly comparisons with topical corticosteroids. If the regulatory agencies' request is not fully addressed or satisfied, getting approval for that region or for specific age groups may become impossible. Is it necessary to claim superiority or non-inferiority in the label? It may be sufficient to include an active comparator just for reference purposes in a phase 2 study. Having topical corticosteroid reference data has many benefits for prescribers and payers. With these factors, you need to negotiate internally and externally, assess several scenarios, and come up with options.

Itch is a key feature of atopic dermatitis and has a tremendous impact on the patient's quality of life. It is hard to expect a patient to adhere to a treatment if their itch does not decrease at an early stage (such as within 1 or 2 weeks) after starting treatment with a new drug. Assessing whether your drug reduces itch and the onset of the effect in phase 2 studies is highly recommended. To claim itch reduction in the label, your phase 3 studies need to meet an itch endpoint using a time-stamped itch numerical rating scale (NRS). The NRS comprises one item and represents the numbers 0 ("no itch") to 10 ("worst imaginable itch"). When using the NRS in adults with moderate to severe atopic dermatitis, a 4-point change in the 11-point itch NRS from baseline is generally agreed to be a clinically meaningful itch reduction for FDA. The timeframe (e.g. 24 hours, 3 days, 1 week) to recall the worst itch or average itch is also a key factor in choosing your endpoints. Acceptability of a 3-point change from baseline for mild to moderate atopic dermatitis or percentage change from baseline should be explored and discussed with the FDA and other relevant regulatory agencies.[167]

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[166] Khattri, Saakshi, Patrick M. Brunner, Sandra Garcet, Robert Finney, Steven R. Cohen, Margeaux Oliva, Riana Dutt, et al. "Efficacy and Safety of Ustekinumab Treatment in Adults with Moderate-to-Severe Atopic Dermatitis." *Experimental Dermatology* 26, no. 1 (2017): 28–35. https://doi.org/10.1111/exd.13112.

[167] Barrett, Amy, Julie Hahn-Pedersen, Nana Kragh, Emily Evans, and Ari Gnanasakthy. "Patient-Reported Outcome Measures in Atopic Dermatitis and Chronic Hand Eczema in Adults." *The Patient* 12, no. 5 (October 2019): 445–59. https://doi.org/10.1007/s40271-019-00373-y.

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Multiple patient reported outcomes (PROs) are available and have been included in atopic dermatitis clinical studies. Considering the burden for patients to complete each assessment, it is necessary to assess how many PROs can be reasonably managed in a study. The FDA requests inclusion of disease-specific PROs for labeling purposes, but the EMA appears to be open to usingthe more general Dermatology Life Quality Index. In addition to discussion with regulatory agencies, acceptability by payers is important for reimbursement. There are international activities involving patients, clinicians, and drug developers to collaboratively standardize the PROs and outcome measures in this area.[168] Getting patients' insight for drug development is becoming a future standard, and the number of PROs is increasing. The PRO validation process can be complex, but use of properly-validated PROs in controlled clinical studies has the greatest chance of being included in the label.[169] Positive PRO data also contributes to the evaluation of risk-benefit and reimbursement decisions.

Atopic dermatitis (like psoriasis) is a chronic inflammatory skin disease and long-term control of flare is an important aspect of disease management. Regulatory agencies want data on long-term safety and maintenance of efficacy of atopic dermatitis treatments. As such, a long-term safety study, which is often conducted open-label for at least 1 year, will be a minimum requirement for approval. For topical drug products, continuous treatment is not necessary, and an intermittent treatment schedule is acceptable. Studies evaluating proactive treatment regimens may also be conducted preapproval or as post-approval (phase 4) studies with the intent of a label update.

The role of the skin microbiome in atopic dermatitis has become a popular topic. There are some drugs in the pipeline specifically targeting normalization of the skin microbiome; however, this may also be achieved when treatment is efficacious, even with drugs not intended to normalize the microbiome. When you visually analyze normalization of microbiome and demonstrate statistical significance for the change from baseline in certain bacteria strains, there may be an opportunity to claim this effect in the label, which may be a differentiation factor for marketing. Discussing

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[168] Harmonising Outcome Measures for Eczema (HOME). "Core Outcome Set and Core Outcome Instruments for Clinical Trials." Accessed October 2019. http://www.homeforeczema.org/.

[169] Food and Drug Administration. *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. Guidance for Industry. December 2009. https://www.fda.gov/media/77832/download.

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and negotiating new endpoints with regulatory agencies requires extensive research and preparation. Drug development is a highly regulated discipline but there is still room for innovation.

Encouraged by the recent introduction of dupilumab (Dupixent®), many other biologics and oral drugs for atopic dermatitis treatment are in the development pipeline. It is expected that the overall treatment landscape for moderate to severe atopic dermatitis will change relatively quickly with these new drugs, and the market will be separated between systemic treatment and topical treatment. Even within the same disease state and severity category, the target patient population varies. For example, tacrolimus ointment and dupilumab injection are both indicated for moderate to severe atopic dermatitis, but tacrolimus is approved for children and dupilumab is only approved for adolescents and adults. Drug developers need to be savvy to grasp the implications of the new treatment landscape and evolving market needs. When applicable, these changes should be discussed with the regulatory agencies and reflected in clinical trial designs. Emergence of new treatment options will also require updates to current treatment guidelines.

Other Inflammatory Skin Diseases

Recent expansions of the indications of immunoinflammatory skin diseases, such as vitiligo and alopecia areata, are partially driven by Janus kinase (JAK) inhibitors.[170] The JAK family of kinases includes JAK1, JAK2, JAK3, and tyrosine kinase 2 (Tyk2). Selective JAK inhibitors have anti-inflammatory properties and have promising effectiveness in treating psoriasis, atopic dermatitis, vitiligo, and alopecia areata. The benefit-risk ratio is an important aspect for any drug approval, but considering the current unmet medical need for treatments for vitiligo and alopecia areata, these indications may have an advantage when assessing the benefit-risk ratio.

There was a public meeting in 2017 to hear the voice of patients with alopecia areata as a part of the FDA's Patient-Focused Drug Development

[170] Shreberk-Hassidim, Rony, Yuval Ramot, and Abraham Zlotogorski. "Janus Kinase Inhibitors in Dermatology: A Systematic Review." *Journal of the American Academy of Dermatology* 76, no. 4 (April 2017): 745-753.e19. https://doi.org/10.1016/j.jaad.2016.12.004.

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Initiative.[171] In the report, it became clear that patients have been dissatisfied with current treatment options and they would prefer an oral medication with fewer side effects. Many skin diseases are sometimes viewed as just a "cosmetic" problem, but the report concluded that alopecia areata is a serious condition with physical, emotional, and social impacts. The voices of these patients will influence drug development. Working together with patients' advocacy groups is now becoming a standard part of drug development. These activities will improve patient acceptance of new treatment options, which should also benefit drug approval and reimbursement.

PF-06651600 was granted breakthrough therapy designation from the FDA for the treatment of patients with alopecia areata. The JAK3 inhibitor demonstrated positive phase 2 results, which were anticipated based on results reported from an investigator-initiated trial that showed favorable results with tofacitinib (Xeljanz®), a JAK1/JAK3 inhibitor.[172] Higher selectivity of PF-06651600 for justJAK3 could improve the safety profile.

For vitiligo treatment, both topical and oral JAK inhibitors are advancing to the late stage of clinical development.[168]

Acne Vulgaris

It is interesting to see the historical differences between acne vulgaris and two major immunoinflammatory skin diseases, namely psoriasis and atopic dermatitis, from the drug-development perspective. While biologics drove drug development in psoriasis and atopic dermatitis, drug development for acne vulgaris shows a very different spectrum. The visibility of new drugs is higher with biologics and systemic drugs, as phase 3 study results are often reported in the highest-ranking journals, such as the New England Journal of Medicine and the Lancet. Topics around topical drugs are more visible in the dermatology journals, regardless of indication. The impact on the marketplace is usually higher with new systemic drugs than new topical drugs, due to the prices. However, if you are interested in topical drug development, the acne field provides many valuable lessons.

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[171] Food and Drug Administration. *The Voice of the Patient. Alopecia Areata*. March 2018. https://www.fda.gov/media/112100/download.

[172] Damsky, William, and Brett A. King. "JAK Inhibitors in Dermatology: The Promise of a New Drug Class." *Journal of the American Academy of Dermatology* 76, no. 4 (April 2017): 736–44. https://doi.org/10.1016/j.jaad.2016.12.005.

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Diagnosis of the type and severity of acne lesions will help direct appropriate therapeutic interventions, as well as focus development of new therapeutics. As described for psoriasis and atopic dermatitis, acne vulgaris is also divided into mild to moderate and moderate to severe categories for drug development purposes. In addition, "severe recalcitrant nodular and conglobate acne" are the most severe and have usually failed other treatment options, thus treatment with oral isotretinoin (e.g. Accutane®) is indicated. Nodules are inflammatory lesions with a diameter of 5 mm or greater. For these types of very severe acne, there are opportunities for oral and even biologic treatment.[173] With the recently evolving understanding that acne vulgaris is also partly an immunoinflammatory condition, biologics may play a larger role. Since we have not yet seen biologics or immunomodulatory oral drugs indicated for acne, it is important to discuss with the FDA and other regulatory authorities about the primary endpoint(s) to achieve agreement before initiating late-phase studies.

The primary endpoints for acne drug development in the US have been IGA success, absolute change in inflammatory lesion counts, and absolute change in non-inflammatory lesion counts. It was not necessarily straightforward to meet all three endpoints owing to the subjective nature of IGA. The number of inflammatory and non-inflammatory lesions may seem like objective endpoints, but the truth is that it is not easy to standardize the way that each investigator counts the lesions. It is not only a visual assessment; palpation of lesions is often required. Standardization and training of the evaluators is key for success in clinical trials and great efforts have been made by experts who consulted the industry throughout discussions with the FDA and other regulatory agencies.[174] It has often been experienced that IGA improvement is not well correlated with inflammatory lesion counts if the investigator was not well trained prior to the clinical trials. A draft Guidance for Industry was published in 2005: the draft was finally finalized in 2018: Acne Vulgaris—Establishing Effectiveness of

[173] Thiboutot, Diane M., Brigitte Dréno, Abdullah Abanmi, Andrew F. Alexis, Elena Araviiskaia, Maria Isabel Barona Cabal, Vincenzo Bettoli, et al. "Practical Management of Acne for Clinicians: An International Consensus from the Global Alliance to Improve Outcomes in Acne." *Journal of the American Academy of Dermatology* 78, no. 2 Suppl 1 (2018): S1-S23.e1. https://doi.org/10.1016/j.jaad.2017.09.078.

[174] Acne Core Outcomes Research Network (ACORN). "For Professionals." Accessed October 2019. https://sites.psu.edu/acnecoreoutcomes/for-professionals/.

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Drugs Intended for Treatment.[175] The final guidance document became simplified from a 17-page document to a 7-page document. In the final guidance, the IGA is defined as follows: the IGA should be an ordinal scale with approximately five severity grades, each grade should be defined by a distinct and clinically relevant morphologic description to minimize interobserver variability, and the definitions of the severity grades should not include numerical ranges of lesions because the IGA scale is intended to be a qualitative assessment of the patient's condition. Further, the IGA scale should be dichotomized to success or failure, with success defined as clear or almost clear skin (grade 0 or 1) and at least a two-grade improvement from baseline; this represents a clinically meaningful outcome. Since there is no single, standardized grading system for acne severity, the FDA is encouraging sponsors to discuss their IGA scales and study designs before trial initiation. There have been many different IGA scales[169] used in clinical studies and discussed with the FDA through the years. FDA also acknowledges that the IGA scale for moderate to severe acne is separate from assessment of nodular/conglobate acne.

Although the finalized guidance document does not clearly mention that the phase 3 study design needs to include three coprimary endpoints to successfully file for acne vulgaris, it says the assessment of treatment effect should be based on both changes in lesion counts and success on the IGA. The FDA makes their viewpoint on the IGA clear as they say that endpoints based on changes in lesion counts and IGA success provide both quantitative and qualitative assessments of acne severity, and thus provide useful complementary information. The Japanese regulatory agency (PMDA) seems to focus more on percentage reductions in total lesion counts, inflammatory lesion counts, and non-inflammatory lesion counts than on absolute changes. When conducting global clinical trials, it is important to negotiate with regulatory authorities in each region of interest. When bridging studies between different regions, efficiency is the key. If a Japanese study will be conducted referencing US studies, it would be more straightforward and efficient to include the Japan preferred primary endpoints as secondary (or even tertiary or exploratory) endpoints in a US study. Otherwise, posthoc analyses need to be done after completion of the studies, which requires additional resources. It is often difficult as the team members who have been familiar with the data have usually moved to different projects or even different companies before the posthoc analyses

[175] Food and Drug Administration. *Acne Vulgaris: Establishing Effectiveness of Drugs Intended for Treatment*. Guidance for Industry. May 2018. https://www.fda.gov/media/71152/download.

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are required. Even if your company is targeting only the US market, you may have alliance partners at later points in different regions. Planning for global drug development may help increase efficiency in the study design.

The FDA recently approved sarecycline (Seysara®), a new tetracycline-derived oral antibiotic, for patients with inflammatory lesions associated with non-nodular moderate-to-severe acne vulgaris. The description of the indication is interesting as it clearly says "non-nodular" moderate-to-severe acne vulgaris. It is evidence that different study endpoints and criteria will be needed in studies for nodular acne vulgaris. Clascoterone, an androgen receptor inhibitor, may also be approved in the near future. Except for these two drugs, the acne drug development field has been lacking new chemical entities.

The results of phase 3 studies with trifarotene cream for moderate facial and truncal acne were recently published.[176]As we write this book, the review by the FDA is ongoing. The indication and label claim approved by the FDA will be of interest because FDA says in the guidance document that efficacy assessments should be limited to the face because it is the most frequent site of involvement, although acne also occurs on the trunk. The co-primary endpoints for trifarotene were IGA success, absolute change in facial inflammatory lesion counts, and absolute change in facial non-inflammatory lesion counts; they included truncal lesion counts as secondary endpoints. Regardless of the indication and label claim, effects on truncal acne are informative for prescribers.

Although new chemical entities are lacking, there are many successes around reformulations and fixed combinations of two active pharmaceutical ingredients (APIs). These areas are of particular interest for topical drug development. Historically, most boutique/niche pharmaceutical companies that have focused on dermatology or skincare have run profitable businesses with reformulations (e.g. ointments, creams, gels, lotions and foams) and the creation of new fixed-combination products. Combinations of topical antibiotics, benzoyl peroxide, and retinoids have demonstrated favorable results. Fixed-combination topical drugs provide patient convenience as well as improved efficacy. The study design always attempts to demonstrate

[176] Tan, Jerry, Diane Thiboutot, Georg Popp, Melinda Gooderham, Charles Lynde, James Del Rosso, Jonathan Weiss, et al. "Randomized Phase 3 Evaluation of Trifarotene 50 mg/g Cream Treatment of Moderate Facial and Truncal Acne." *Journal of the American Academy of Dermatology* 80, no. 6 (June 2019): 1691–99. https://doi.org/10.1016/j.jaad.2019.02.044.

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that the fixed combination is superior or at least noninferior to each single agent, as seen in the label of Epiduo® (adapalene and benzoyl peroxide) gel 0.1%/2.5%.[177] Then another reformulation with a higher concentration of adapalene was developed: Epiduo Forte® (adapalene and BPO) gel 0.3%/2.5% demonstrated superiority over Epiduo, thus there was no need to compare Epiduo Forte with each single agent.[178]

Market penetration of topical dermatological drugs often depends on aesthetic aspects of the vehicle, such as texture, greasiness, and spreadability. Boutique/niche pharmaceutical companies specialized in dermatology and/or skincare typically have more strength in this area than big pharma.

Pemphigus Vulgaris

Pemphigus vulgaris is a rare autoimmune disease that causes blisters on the skin and mucous membranes. The most common first line therapy for pemphigus vulgaris is systemic corticosteroids. Individually, rare diseases do not affect a large number of people, and there are few approved treatment options. Historically, most therapies have been used off-label, with very limited data on the efficacy and safety of the product for the relevant indication and patient population.

Rituximab (Rituxan®), a monoclonal antibody, was approved as an orphan drug for the treatment of adult patients with moderate-to-severe pemphigus vulgaris in 2018. The FDA granted Rituxan Priority Review, Breakthrough Therapy Designation, and Orphan Drug Designation for the treatment of pemphigus vulgaris. The FDA approval was based on data from the Ritux 3 trial, a Roche-supported, randomized, controlled trial conducted in France that used Roche-manufactured, European Union (EU)-approved

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[177] Epiduo (adapalene and benzoyl peroxide) Gel 0.1%/2.5% For topical use [prescribing information]. Fort Worth, Texas: Galderma Laboratories, LP; January 2013. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022320s004lbl.pdf.

[178] Stein Gold, Linda, Jonathan Weiss, Maria Jose Rueda, Hong Liu, and Emil Tanghetti. "Moderate and Severe Inflammatory Acne Vulgaris Effectively Treated with Single-Agent Therapy by a New Fixed-Dose Combination Adapalene 0.3 %/Benzoyl Peroxide 2.5 % Gel: A Randomized, Double-Blind, Parallel-Group, Controlled Study." *American Journal of Clinical Dermatology* 17, no. 3 (June 2016): 293–303. https://doi.org/10.1007/s40257-016-0178-4.

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rituximab product as the clinical trial material.[179] The study compared the Ritux 3 regimen (EU-approved rituximab product plus short-term corticosteroids) with corticosteroids alone as first-line treatment in patients with newly-diagnosed, moderate-to-severe pemphigus.[180] The study was prepared as an investigator-initiated trials; funding originated from the French Ministry of Health, the French Society of Dermatology, and Roche. Information on the US label reflects this information: US approval was based on "non-U.S.-licensed rituximab in combination with short-term prednisone compared to prednisone monotherapy as first-line treatment in 90 newly diagnosed adult patients with moderate to severe pemphigus (74 pemphigus vulgaris and 16 pemphigus foliaceus)".[181] Although approval was based on the controlled French study, it is likely that information from years of off-label treatment cases in the US was gathered and analyzed by the applicant for the FDA.

Compared with the diseases already discussed in this chapter, there are many different aspects to consider before moving forward with development of a rare disease treatment. From a business perspective, developing a medication for a rare disease indication will not generate a large return on investment, which is a major reason why not many companies go into the rare disease area. In the United States, a rare disease is defined as a condition that affects fewer than 200,000 people. This definition was created by Congress in the Orphan Drug Act of 1983. Rare diseases became known as "orphan" diseases because pharmaceutical companies were not interested in developing treatments for those diseases. The definition of rare disease is slightly different in EU, and a disease is considered rare if fewer than five in 10,000 people are afflicted. In 2000, the EU's orphan designation program was launched to encourage companies to research and develop medicines for rare diseases. By the end of 2017, over 1,900 medicines had been granted orphan status, which gives

[179] Genentech. "Press Releases, Thursday, Jun 7, 2018." https://www.gene.com/media/press-releases/14727/2018-06-07/fda-approves-genentechs-rituxan-rituxima.

[180] Joly, Pascal, Maud Maho-Vaillant, Catherine Prost-Squarcioni, Vivien Hebert, Estelle Houivet, Sébastien Calbo, Frédérique Caillot, et al. "First-Line Rituximab Combined with Short-Term Prednisone versus Prednisone Alone for the Treatment of Pemphigus (Ritux 3): A Prospective, Multicentre, Parallel-Group, Open-Label Randomised Trial." *Lancet (London, England)* 389, no. 10083 (May 20, 2017): 2031–40. https://doi.org/10.1016/S0140-6736(17)30070-3.

[181] Rituxan (rituximab) injection, for intravenous use [prescribing information]. South San Francisco, California: Genentech, Inc.; November 2019. https://www.gene.com/download/pdf/rituxan_prescribing.pdf.

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access to specific incentives that make it more attractive for companies to develop these treatments.[182] Conducting clinical trials for regulatory approval requires a significant amount of time and money, while future sales are unlikely to cover the development costs. As the pharmaceutical companies are for-profit, it is difficult to support the business assessment to go into the arena. This atmosphere is changing.

The Orphan Drug Act created financial incentives to encourage companies to develop new drugs for rare diseases. The FDA Office of Orphan Products Development was created to advance the evaluation and development of products that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions. One incentive for sponsors to develop products for rare diseases is the Orphan Product Clinical Trials Grant. Another incentive to boost development is a priority review voucher, which may be granted to sponsors of applications for the treatment of certain tropical diseases or for treatment of rare pediatric diseases.[183,184]The US Congress created the priority review voucher program in 2007. The applicant may use the voucher for their own product or sell the voucher to another company; previous vouchers have sold for 50 to 100 million US dollars. With the voucher, the FDA will review the marketing application within 6 months of receipt (compared with 10 months under standard review). This accelerated review leads to early introduction of the drug to the market, resulting in early revenue generation that sufficiently covers the cost of buying the voucher. As of December 31, 2019, 34 vouchers had been issued. Since 1983, with these initiatives, the FDA has granted nearly 4,800 orphan drug designations.

Researchers who are interested in seeking effective therapies for specific rare diseases may begin with investigator-initiated trials/research (IIT/IIR) by creating research networks and operating the studies with government or non-profit funding. The National Institutes of Health (NIH) supports

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[182] European Medicines Agency. Development of medicines for rare diseases. August 2018. https://www.ema.europa.eu/en/news/development-medicines-rare-diseases.

[183] Food and Drug Administration, Office of Orphan Products Development. "Developing Products for Rare Diseases & Conditions." https://www.fda.gov/industry/developing-products-rare-diseases-conditions.

[184] Food and Drug Administration. *Rare Pediatric Disease Priority Review Vouchers*. Guidance for Industry (Draft). July 2019. https://www.fda.gov/media/90014/download.

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research for rare diseases by several activities, including funding and facilitating research networks.[185]

Running clinical trials for rare diseases, including pemphigus vulgaris, is not only operationally but scientifically challenging. Approval of any drug (even for a rare disease) must be based on substantial evidence of effectiveness and sufficient information to conclude that the drug is safe from adequate and well-controlled clinical studies. One of the largest issues is extremely low recruitment into clinical studies—this is partly due to rarity of the disease; the study centers being likely academic referral centers, so their patients may not be located in close proximity; and potential competition from other studies trying to recruit the same limited patient population. Designing the clinical trials to demonstrate a statistically significant difference between the active treatment and placebo may need a large sample size that is operationally unfeasible. The FDA acknowledges these challenges and is working together with the industry and academia to find solutions.[186]

Having a placebo comparator group is critical to demonstrate scientific validity, but may present an ethical concern in some situations. One solution is to use a historical control. The draft guidance document on rare diseases is touching on a natural history study to develop and use a historical control. As natural history studies take time to design, execute, and discuss with the FDA, the studies should be part of early drug development. When a natural history study or historical control is not an option, a placebo-controlled study may be conducted using a modified study design, such as randomized withdrawal, crossover, adaptive design with interim analysis, or an open-label extension after data for the primary endpoint are collected (this may be worth considering as it will provide an opportunity for the patient to receive the investigational drug). If a standard of care is established and has historical data, using the standard of care as the control group in lieu of placebo may be appropriate. Some studies also continue the standard of care as background therapy (e.g. corticosteroids for pemphigus vulgaris) and use

[185] Genetic and Rare Diseases Information Center (GARD) – an NCATS Program. "FAQs About Rare Diseases" Accessed October 2019. https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases.

[186] Food and Drug Administration. *Rare Diseases: Common Issues in Drug Development*. Guidance for Industry (Draft). February 2019. https://www.fda.gov/media/120091/download.

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an add-on design to evaluate the effects of the investigational drug versus placebo, while still providing treatment for all patients.

Development of orphan designated drugs may follow different development and approval pathways than standard products; it is therefore important to discuss all options with the regulatory agencies at an early stage of development. Some of the FDA programs for development of treatments for rare diseases also facilitate frequent interactions with the agency to keep the development program on track. Application of mobile technology for rare disease clinical trials will be helpful from both the patient and caregiver perspective, especially because many rare diseases are treated at academic referral centers, which may be a significant distance from the patient's home. Remember: any aspect of study design that is outside the traditional structure should first be discussed with the regulatory authorities.

Androgenetic (Androgenic) Alopecia

While alopecia areata may be viewed as a medical condition, androgenetic alopecia is frequently considered a cosmetic condition. This opinion limits approved treatment options and makes insurance coverage and reimbursement highly unlikely.

Minoxidil (Rogaine®) is the first and only topical medication approved for androgenetic alopecia in men and women. It is available in 2% and 5% concentrations, applied to the scalp as a liquid or foam. Minoxidil 2% solution was approved by the FDA for men in 1988 and for women in 1992. Since then, additional renditions have been created, including a 5% solution and 5% foam. Rogaine was converted from a prescription drug to over-the-counter (OTC) status in 1996. There has not been a new topical medication for androgenetic alopecia approved for decades, but ATI-502, an investigational topical JAK1/JAK3 inhibitor, is currently in the phase 2 clinical trial stage for adult women and men with androgenetic alopecia.

Finasteride (Propecia®) is a leading oral medication to treat androgenetic alopecia. Finasteride is a 5α-reductase inhibitor that was originally approved in 1992 at a 5 mg dose for prostate hyperplasia, and then approved in 1997 at a lower, 1 mg dose for the treatment of androgenetic alopecia in men only.[187] The most common adverse reactions (>1%) are decreased

[187] Propecia (finasteride) tablets for oral use [prescribing information]. Whitehouse Station, New Jersey: Merck & Co., Inc.; April 2012.

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libido, erectile dysfunction, and ejaculation disorder; these reactions were also reported in the placebo groups during clinical trials. For example, decreased libido was reported in 1.8% of patients treated with finasteride 1 mg and 1.3% of patients treated with placebo. However, when combined, these adverse events are consistently higher in the active group. Integrated analysis of clinical adverse experiences showed that 3.8% (36 of 945 men) treated with finasteride 1 mg had reported one or more of these adverse experiences compared with 2.1% (20 of 934 men) treated with placebo (p=0.04). The label shows p-value comparing active and placebo for safety, which is not so common. As this drug treats cosmetic issues, the FDA seems to have felt that risk-benefit assessment should be more stringent than for diseases that need to be treated; treatment for cosmetic issues that potentially harms the patient may not be needed.

Dutasteride is an inhibitor of both type I and type II 5α-reductase. There are studies showing the superiority of dutasteride over finasteride in the treatment of hair loss.[188,189] However, dutasteride is not approved for the treatment of androgenetic alopecia in the US or EU. It is approved in Japan and South Korea. This may be due to ethnic and cultural differences between the US and Asian countries. Androgenetic alopecia affects approximately 80% of Caucasian males and is very common in the US. On the other hand, it only affects around 20% of males in the Asian population.[190] Therefore, Asian males may have a greater psychosocial

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https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020788s020s021s023lbl.pdf.

[188] Gubelin Harcha, Walter, Julia Barboza Martínez, Tsen-Fang Tsai, Kensei Katsuoka, Makoto Kawashima, Ryoji Tsuboi, Allison Barnes, Geraldine Ferron-Brady, and Dushen Chetty. "A Randomized, Active- and Placebo-Controlled Study of the Efficacy and Safety of Different Doses of Dutasteride versus Placebo and Finasteride in the Treatment of Male Subjects with Androgenetic Alopecia." *Journal of the American Academy of Dermatology* 70, no. 3 (March 2014): 489-498.e3. https://doi.org/10.1016/j.jaad.2013.10.049.

[189] Shanshanwal, Sujit J. S., and Rachita S. Dhurat. "Superiority of Dutasteride over Finasteride in Hair Regrowth and Reversal of Miniaturization in Men with Androgenetic Alopecia: A Randomized Controlled Open-Label, Evaluator-Blinded Study." *Indian Journal of Dermatology, Venereology and Leprology* 83, no. 1 (February 2017): 47–54. https://doi.org/10.4103/0378-6323.188652.

[190] Wang, T. L., C. Zhou, Y. W. Shen, X. Y. Wang, X. L. Ding, S. Tian, Y. Liu, et al. "Prevalence of Androgenetic Alopecia in China: A Community-Based Study in Six Cities." *The British Journal of Dermatology* 162, no. 4 (April 2010): 843–47. https://doi.org/10.1111/j.1365-2133.2010.09640.x.

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burden, and the risk-benefit ratio may be viewed differently in Asian countries than in the US or EU.

Although persistent sexual side effects associated with finasteride have been called post-finasteride syndrome, controlled clinical data show a low incidence of sexual side effects that resolve on cessation of treatment.[191] Several large, population-based, long-term, placebo-controlled studies have not demonstrated clear evidence of the negative effect of the 5α-reductase inhibitor on erectile function.[192] A nocebo effect has been suggested.[193] A nocebo effect occurs when a patient anticipates a side effect of a medication; they can suffer that effect even if the medication has no such effect, while a placebo effect is considered to occur when positive expectations improve an outcome. Although sexual dysfunctions observed in patients with androgenetic alopecia treated with 5α-reductase inhibitors is truly a nocebo effect, the pharmaceutical companies do not want to go through judicatory processes, unless it is absolutely necessary. This may be a reason that some companies have not sought approval of 5α-reductase inhibitors for androgenetic alopecia in more regions.

External Genital Warts / Condyloma Acuminatum

External genital warts (EGW), also known as condyloma acuminata, are extremely common, with between 500,000 to one million new cases diagnosed each year in the United States alone. Human papillomavirus types 6 and 11 rarely give rise to cervical cancers, but are responsible for 90% of genital wart cases. The disease is highly contagious and sexual contact with an HPV-infected individual has a 75% chance of developing

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[191] Gupta, Aditya K., and Andrew Charrette. "The Efficacy and Safety of 5α-Reductase Inhibitors in Androgenetic Alopecia: A Network Meta-Analysis and Benefit-Risk Assessment of Finasteride and Dutasteride." *The Journal of Dermatological Treatment* 25, no. 2 (April 2014): 156–61. https://doi.org/10.3109/09546634.2013.813011.

[192] Anitha, B., Arun C. Inamadar, and S. Ragunatha. "Finasteride-Its Impact on Sexual Function and Prostate Cancer." *Journal of Cutaneous and Aesthetic Surgery* 2, no. 1 (January 2009): 12–16. https://doi.org/10.4103/0974-2077.53093.

[193] Mondaini, Nicola, Paolo Gontero, Gianluca Giubilei, Giuseppe Lombardi, Tommaso Cai, Andrea Gavazzi, and Riccardo Bartoletti. "Finasteride 5 Mg and Sexual Side Effects: How Many of These Are Related to a Nocebo Phenomenon?" *The Journal of Sexual Medicine* 4, no. 6 (November 2007): 1708–12. https://doi.org/10.1111/j.1743-6109.2007.00563.x.

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EGW.[194] The current treatment options are largely centered upon removal of the warts rather than elimination of the underlying viral infection.

Podophyllotoxin (e.g. Condylox®) is a purified extract of the podophyllum plant, which binds to cellular microtubules, inhibits mitotic division, and induces necrosis of warts that is maximal three to five days after application. The drug was FDA approved in 1997 for self-administration. Podophyllotoxin is available as a solution, cream, or gel and must be applied twice daily for three consecutive days of the week, for a maximum of four weeks. Shallow erosions occur as the lesions necrotize and heal within a few days. Randomized, placebo-controlled trials have demonstrated successful clearance rates ranging from 45% to 77%. Podophyllotoxin is also associated with rates of recurrence around 40%. Local skin reactions are very common and include pain, inflammation, erosion, burning, or itching at the application site.[195]

Sinecatechins is a botanical extract approved in 2006 by the FDA for the treatment of genital warts, making it the first botanical to officially receive medical approval. The active ingredient is a green tea extract containing sinecatechins, which is thought to possess antioxidant, antiviral, and antitumor effects. Sinecatechins cream is applied topically to warts three times a day for up to four months. Typically, if an improvement is not seen within a few weeks, the treatment is stopped, and another option is tried.[196] Although it is mild, 20% of patients reported adverse events such as redness, burning, itching, and pain at the application site.

Imiquimod 5% cream (Aldara®) is a patient-applied topical immunomodulatory agent, which first received its indication for the treatment of EGW in 1997. It has since been used in the treatment of a variety of skin conditions, including superficial basal cell carcinomas and actinic keratoses, both indications being approved by FDA in 2004.

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[194] Cates, W. "Estimates of the Incidence and Prevalence of Sexually Transmitted Diseases in the United States. American Social Health Association Panel." *Sexually Transmitted Diseases* 26, no. 4 Suppl (April 1999): S2-7. https://doi.org/10.1097/00007435-199904001-00002.

[195] Yanofsky, Valerie R., Rita V. Patel, and Gary Goldenberg. "Genital Warts: A Comprehensive Review." *The Journal of Clinical and Aesthetic Dermatology* 5, no. 6 (June 2012): 25–36.

[196] Meltzer, Sara M., Bradley J. Monk, and Krishnansu S. Tewari. "Green Tea Catechins for Treatment of External Genital Warts." *American Journal of Obstetrics and Gynecology* 200, no. 3 (March 2009): 233.e1-7. https://doi.org/10.1016/j.ajog.2008.07.064.

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Although its precise mechanism of action remains unclear, imiquimod is believed to activate immune cells by binding to the membranous toll-like receptors. For the treatment of EGW, imiquimod is applied at bedtime three times per week for up to 16 weeks. Commonly encountered local skin reactions, such as itching, erythema, burning, irritation, tenderness, ulceration, and pain, have been long-standing issues with the 5% creams leading to poor patient tolerance. The FDA later approved imiquimod 3.75% cream for the treatment of EGW and imiquimod 2.5% cream for treatment of actinic keratosis (Zyclara®). The motivation for lowering the concentrations was likely to improve tolerability, which would increase patients' adherence to treatment, and thus lead to comparable efficacy with 5% in the real-world setting. The recurrence rate of EGW after treatment was low at around 15%.

Both podophyllotoxin and imiquimod cause notable adverse events of local skin reactions. Sinecatechins also are associated with mild local skin reactions. These reactions seem to be due, at least in part, to application on sensitive areas, as well as the pharmacological effects. Local skin reactions are also concerning when the drug is applied on the face, owing to the risk of scarring. As imiquimod has indications for treatment of EGW as well as actinic keratosis (frequently occur on face), local skin reactions are highlighted in the warnings and precautions section of the label and separate analyses of the local skin reactions are presented. There is no standardized approach or grading system to assess local skin reactions, which complicates efforts to compare reactions between different products. The sponsor should be prepared to assess and analyze local skin reactions in the protocol and the statistical analysis plan. It is desirable to have new topical medications that have a lower incidence of local skin reactions.

Nitric oxide-releasing gel (SB206) has been investigated for the treatment of EGW in a phase 2 study;[197] phase 3 studies are planned.

For EGW clinical studies, the FDA has been clear that the primary efficacy endpoint should be the proportion of patients achieving complete clearance of existing and new warts in the treatment area during the study. Although the US label includes partial clearance for the Zyclara actinic

[197] Tyring, Stephen K., Theodore Rosen, Brian Berman, Nathan Stasko, Todd Durham, and Tomoko Maeda-Chubachi. "A Phase 2 Controlled Study of SB206, a Topical Nitric Oxide-Releasing Drug for Extragenital Wart Treatment." *Journal of Drugs in Dermatology: JDD* 17, no. 10 (October 1, 2018): 1100–1105.

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keratosis section, partial clearance was not included for the EGW section.[198] The recurrence rate is generally evaluated over a 12-week follow-up period.[199]

Molluscum Contagiosum

Molluscum contagiosum is a predominantly pediatric disease, which is frequently treated with mechanical procedures (e.g. curettage, cryotherapy) but sometimes with off-label topical treatment (e.g. imiquimod, cantharidin). There are no approved topical therapies in the US as of 2019. The disease is caused by molluscum contagiosum virus of the pox virus family. The disease is highly contagious by direct skin contact among children and family members, but usually demonstrates spontaneous resolution. However, when many lesions are present, autoinoculation occurs by scratching and increases the number of lesions (possibly as many as 100). When the number of lesions increases, spontaneous resolution, which would normally take place after about 2 months for a solitary lesion, takes as long as 2 years. While molluscum contagiosum is predominantly a children's disease, immunocompromised patients, particularly HIV-infected patients demonstrate a severe form of molluscum contagiosum. For these patients, spontaneous resolution is not expected, and new therapies are needed. For immunocompetent adolescents and adults, sexually transmitted infection is the main cause of the disease.

Caregivers take children to pediatricians first, but their standard of care is "wait and see" for mild cases or referral to a pediatric dermatologist if more severe or bothersome. Mechanical procedures often cause pain and instill fear in children; pediatricians want to avoid damaging their doctor-patient relationship because they anticipate a long-term relationship with the child. Mechanical procedures are therefore primarily carried out in a dermatologist's office. If new, pain-free, topical treatments are developed, it is likely that such treatments will be used at pediatricians' offices as well as dermatologists' offices.

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[198] Zyclara (imiquimod) cream, 3.75% [prescribing information]. Bristol, Tennessee: Graceway Pharmaceuticals, LLC; March 2011. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201153s000,022483s001lbl.pdf.

[199] Aldara (imiquimod) Cream, 5% [prescribing information]. Bristol, Tennessee: Graceway Pharmaceuticals, LLC; October 2010. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020723s022lbl.pdf.

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Imiquimod 5% cream was evaluated for the treatment of molluscum contagiosum in three randomized, multicenter, vehicle (placebo)-controlled clinical trials (one phase 2 and two phase 3 studies). In total, 532 children were randomized to the imiquimod arms and 295 children were randomized to the vehicle arms. Treatment frequency and duration varied from daily for 8 weeks to 3 times weekly for 16 weeks. Outcome assessments were lesion clearance, lesion counts, time to complete clearance, and adverse events up to 28 weeks after the start of treatment. It is assumed that resolution of application site reactions and recurrences were also assessed during the follow-up period. These studies showed that imiquimod 5% was not efficacious compared with vehicle, and the frequency of application site reactions was higher with imiquimod.[200] Development was discontinued. It is very interesting to see that the US label states imiquimod cream has been evaluated in children ages 2 to 12 years with molluscum contagiosum and the studies failed to demonstrate efficacy.[201] The background reason is probably because the studies were conducted under the Agency's Written Request (see Chapter 5). Although imiquimod was not efficacious for this indication, the imiquimod study designs have set the stage for the drug development for both efficacy and safety in clinical trials for molluscum contagiosum and have become a standard for the study design.

Cantharidin has been used off-label for more than 50 years, but studies validating its safety and efficacy have been limited. Cantharidin is a vesicant that is naturally derived from the blister beetle, has a long track record of being used to treat primarily molluscum contagiosum and common warts. Although not approved by the FDA, cantharidin has been available through a variety of compounding sources without standardization of manufacturing, formulation, or method of application.[202] The standardization was explored by a company in accordance with Good Manufacturing Practices (GMP),

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[200] Wouden, Johannes C. van der, Renske van der Sande, Emma J. Kruithof, Annet Sollie, Lisette Wa van Suijlekom-Smit, and Sander Koning. "Interventions for Cutaneous Molluscum Contagiosum." *The Cochrane Database of Systematic Reviews* 5 (17 2017): CD004767. https://doi.org/10.1002/14651858.CD004767.pub4.

[201] Zyclara (imiquimod) cream, 3.75% [prescribing information]. Bristol, Tennessee: Graceway Pharmaceuticals, LLC; March 2011. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201153s000,022483s001lbl.pdf.

[202] Del Rosso, James Q., and Leon Kircik. "Topical Cantharidin in the Management of Molluscum Contagiosum: Preliminary Assessment of an Ether-Free, Pharmaceutical-Grade Formulation." *The Journal of Clinical and Aesthetic Dermatology* 12, no. 2 (February 2019): 27–30.

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and they have developed a novel drug-device combination containing a standardized 0.7% w/v cantharidin solution (VP-102 solution) for treatment of molluscum contagiosum. The results of a phase 2, open-label, pilot study evaluating this specific cantharidin 0.7% solution exhibited promising preliminary efficacy and safety results,[203] and the company subsequently conducted phase 3 studies with VP-102 Film-Forming Solution in a prefilled applicator. Treatment was applied to the area(s) affected with molluscum in the clinic once every 21 days. The phase 3 double-blind studies were conducted in 528 patients two years of age and older. Each trial demonstrated superior efficacy of VP-102 compared with placebo with statistically significant differences on the primary endpoint of complete clearance of all treatable molluscum lesions. At the end of the 12-week studies, around 50% of patients treated with VP-102 achieved complete clearance versus around 15% of patients treated with placebo. Adverse effects were frequent, and almost all patients had application site reactions such as vesicles (~100%) and pain (~60%), but they were mostly expected events due to the blistering properties of the drug.

Nitric oxide-releasing gel (SB206) was investigated for the treatment of molluscum in a phase 2 study with promising results.[204] It is currently being investigated in phase 3 studies. Since the study population is predominantly pediatric patients, timely agreement with regulatory agencies on the pediatric study plan is critical to avoid delaying the program. As the disease resolves spontaneously without treatment, which sometimes takes more than a year, the FDA may require more stringent safety assessments than short-term infectious skin conditions. The primary efficacy endpoint is the proportion of patients achieving complete clearance at week 12. This primary endpoint has not been changed since imiquimod was investigated. The FDA's view has been clear that only complete clearance of the molluscum contagiosum is clinically meaningful.

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[203] Guzman, Anthony K., David O. Schairer, Jessica L. Garelik, and Steven R. Cohen. "Safety and Efficacy of Topical Cantharidin for the Treatment of Pediatric Molluscum Contagiosum: A Prospective, Randomized, Double-Blind, Placebo-Controlled Pilot Trial." *International Journal of Dermatology* 57, no. 8 (August 2018): 1001–6. https://doi.org/10.1111/ijd.14079.

[204] Hebert, Adelaide A., Elaine C. Siegfried, Todd Durham, Emily N. de León, Teresa Reams, Elizabeth Messersmith, and Tomoko Maeda-Chubachi. "Efficacy and Tolerability of an Investigational Nitric Oxide-Releasing Topical Gel in Patients with Molluscum Contagiosum: A Randomized Clinical Trial." *Journal of the American Academy of Dermatology*, October 3, 2019. https://doi.org/10.1016/j.jaad.2019.09.064.

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Hyperhidrosis

Hyperhidrosis is a condition defined by excessive sweat production, greater than considered necessary for thermoregulatory needs. Clinically, hyperhidrosis is diagnosed when excess sweating creates significant emotional, physical, or social discomfort, causing a negative impact on the patient's quality of life. This condition may affect at least 4.8% of the US population.[205] The etiology may stem from a complex autonomic nervous system dysfunction, resulting in neurogenic overactivity of otherwise normal eccrine sweat glands, or may be a result of aberrant central control of emotions. This condition is categorized as primary or secondary. Approximately 93% of patients have primary hyperhidrosis, of whom >90% have a typical focal and bilateral distribution affecting the axillae, palms, soles, and craniofacial areas. Secondary hyperhidrosis presents in a more generalized and asymmetric distribution, and is generated by various underlying diseases or medications.

Topical aluminum chloride solution (such as Drysol®) is the initial treatment in most cases of primary focal hyperhidrosis. Botulinum toxin injection (onabotulinumtoxinA; BOTOX®) is considered first- or second-line treatment for axillary, palmar, plantar, or craniofacial hyperhidrosis. Iontophoresis (passing of an ionized substance, such as water, through the skin by application of a direct electrical current) should be considered for treating hyperhidrosis of the palms and soles. Local microwave therapy (miraDry®) is a newer treatment option for axillary hyperhidrosis. Local surgery and endoscopic thoracic sympathectomy may be considered in severe cases that have not responded to topical or medical therapies.[206]

Oral anticholinergics (such as oxybutynin) are useful adjuncts in severe cases of hyperhidrosis when other treatments fail, but usage is limited by anticholinergic side effects such as dry mouth and blurred vision. Oxybutynin is approved for overactive bladder and is used off-label for the treatment of both focal and generalized hyperhidrosis. A number of clinical

[205] Nawrocki, Shiri, and Jisun Cha. "The Etiology, Diagnosis, and Management of Hyperhidrosis: A Comprehensive Review: Etiology and Clinical Work-Up." *Journal of the American Academy of Dermatology* 81, no. 3 (September 2019): 657–66. https://doi.org/10.1016/j.jaad.2018.12.071.

[206] McConaghy, John R., and Daniel Fosselman. "Hyperhidrosis: Management Options." *American Family Physician* 97, no. 11 (2018): 729–34.

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trials have been conducted to demonstrate short- and long-term efficacy for various affected sites.[207]

Clinical trials for axillary hyperhidrosis should enroll patients 9 years of age and older, as the onset of hyperhidrosis may occur during adolescence. Clinical trials should also exclude medications that may cause secondary hyperhidrosis such as selective serotonin and norepinephrine reuptake inhibitors, cholinergic agents, selective estrogen receptor modulators, and hypoglycemic agents.

The most commonly used objective assessment of hyperhidrosis is measurement of gravimetric sweat production (GSP), generally from the axillae and/or palms, which provides the quantitative rate of sweat production as mg per minute. GSP is measured by first drying the skin surface (e.g. palm or axilla), applying a preweighed filter paper to the area for a measured period of time, then weighing the paper again, and calculating the rate of sweat production. The criteria for inclusion into axillary hyperhidrosis clinical trials that is recommended by the International Hyperhidrosis Society is >20 mg/min (or >100 mg over 5 minutes) for men and >10 mg/min (or >50 mg over 5 minutes) for women.[208] The normal GSP for palmar hyperhidrosis is approximately 30 to 40 mg/min; therefore, GSP inclusion criteria for clinical trials in palmar hyperhidrosis are generally higher than for axillary.[204]

In addition to GSP, the quality-of-life and improvement of impaired daily activities should be assessed to confirm the diagnosis as well as to evaluate the impact of treatment. A PRO should be included in pivotal efficacy trials as a co-primary endpoint. FDA generally prefers for the PRO measures to be disease specific. Currently available instruments include the Dermatology Life Quality Index (DLQI; generally modified for sweating)[209] or the 4-point Hyperhidrosis Disease Severity Scale (HDSS).[210] However, updated PROs that evaluate the severity and impact of hyperhidrosis have

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[207] Campanati, Anna, Stamatis Gregoriou, George Kontochristopoulos, and Annamaria Offidani. "Oxybutynin for the Treatment of Primary Hyperhidrosis: Current State of the Art." *Skin Appendage Disorders* 1, no. 1 (March 2015): 6–13. https://doi.org/10.1159/000371581.

[208] International Hyperhidrosis Society. "Diagnosis Guidelines." Accessed October 2019. https://www.sweathelp.org/about-hyperhidrosis/diagnosis-guidelines.html.

[209] Dermatology Life Quality Index (DLQI). Accessed October 2019. http://www.bad.org.uk/shared/get-file.ashx?id=1653&itemtype=document.

[210] International Hyperhidrosis Society. "Hyperhidrosis Disease Severity Scale." Accessed October 2019. https://www.sweathelp.org/pdf/HDSS.pdf.

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been developed for more recent drug approvals. Sponsors should consult with the FDA prior to phase 2 as to the appropriateness of the proposed PRO in pivotal efficacy studies. The use of outcome measures that have already been validated is generally recommended. However, the drug developer may want to develop a different type of PRO or may need to develop a new assessment if a suitable one is not available. In such a circumstance, the drug developer must consult the relevant guidance documents and discuss PRO development with the FDA early in the development program.[211] You cannot discount the time-consuming process of developing and validating a new PRO.

The efficacy and safety of BOTOX for the treatment of primary axillary hyperhidrosis were evaluated in two randomized, multicenter, double-blind, placebo-controlled studies.[212] Adult patients with persistent primary axillary hyperhidrosis who scored 3 or 4 on a HDSS, and who produced at least 50 mg of sweat in each axilla at rest over 5 minutes were recruited. Patients were evaluated at 4-week intervals. Study responders were defined as patients who showed at least a 2-grade improvement from baseline value on the HDSS. Resting axillary sweat production was assessed by weighing a filter paper held in the axilla over a period of 5 minutes. Sweat production responders were those patients who demonstrated a reduction in axillary sweating from baseline of at least 50% at week 4. The criteria for responders for both PRO and GSP are generally considered as the primary endpoints for products recently improved as well as those currently in development. Secondary endpoints, such as mean absolute change in GSP, are also important to understand the treatment effect.

Glycopyrronium topical cloth (Qbrexza) was approved by the FDA in 2018 for treating primary axillary hyperhidrosis in adults and children who are at least 9 years old.[213] The approval was based on the duplicated phase 3

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[211] Food and Drug Administration. *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. Guidance for Industry. December 2009. https://www.fda.gov/media/77832/download.

[212] Botox (onabotulinumtoxinA) for injection [prescribing information]. Irvine, California: Allergan, Inc.; August 2011. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103000s5232lbl.pdf.

[213] Qbrexa (glycopyrronium) cloth, 2.4%, for topical use [prescribing information]. Menlo Park, California: Dermira, Inc.; June 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210361lbl.pdf.

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studies, ATMOS-1 and ATMOS-2.[214] The coprimary endpoints were responder rate (≥4-point improvement from baseline) on item 2 (severity of sweating) of the Axillary Sweating Daily Diary (ASDD), which is a newly developed PRO measure, and absolute change from baseline in axillary GSP at week 4. The ASDD was developed in consultation with the US FDA and in consideration of FDA PRO guidance to assess severity, impact, and bothersomeness of axillary hyperhidrosis.[215]Although topically applied, anticholinergic side effects such as dry mouth, mydriasis, urinary hesitation, dry throat, dry eye, dry skin, and constipation were reported. Other topical anticholinergics, such as sofpironium bromide (BBI-4000) and umeclidinium, have also been studied for palmar and axillary hyperhidrosis.[216,217,218,219,220]

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[214] Glaser, Dee Anna, Adelaide A. Hebert, Alexander Nast, William P. Werschler, Lawrence Green, Richard Mamelok, Janice Drew, John Quiring, and David M. Pariser. "Topical Glycopyrronium Tosylate for the Treatment of Primary Axillary Hyperhidrosis: Results from the ATMOS-1 and ATMOS-2 Phase 3 Randomized Controlled Trials." *Journal of the American Academy of Dermatology* 80, no. 1 (January 2019): 128-138.e2. https://doi.org/10.1016/j.jaad.2018.07.002.

[215] Nelson, L. M., D. DiBenedetti, D. M. Pariser, D. A. Glaser, A. A. Hebert, H. Hofland, J. Drew, D. Ingolia, K. K. Gillard, and S. Fehnel. "Development and Validation of the Axillary Sweating Daily Diary: A Patient-Reported Outcome Measure to Assess Axillary Sweating Severity." *Journal of Patient-Reported Outcomes* 3, no. 1 (September 5, 2019): 59. https://doi.org/10.1186/s41687-019-0148-8.

[216] Brickell Biotech, Inc. "Safety and Efficacy Study of Sofpironium Bromide in Subjects with Axillary Hyperhidrosis (BBI-4000-CL-301) (Cardigan I)." ClinicalTrials.Gov. Accessed December 14, 2019. https://clinicaltrials.gov/ct2/show/NCT03836287.

[217] Brickell Biotech, Inc. "Safety and Efficacy Study of Sofpironium Bromide in Subjects with Axillary Hyperhidrosis (BBI-4000-CL-302) (Cardigan II)." ClinicalTrials.Gov. Accessed December 14, 2019. https://clinicaltrials.gov/ct2/show/NCT03948646.

[218] "A Safety, Tolerability and Preliminary Efficacy Study of BBI-4000 Gel in Subjects with Palmar Hyperhidrosis." ClinicalTrials.Gov. Accessed October 2019. https://clinicaltrials.gov/ct2/show/NCT02682238.

[219] "A Study to Evaluate Clinical Effect, Pharmacokinetics, Safety, and Tolerability of Umeclidinium in Palmar Hyperhidrosis Subjects." ClinicalTrials.Gov. Accessed October 2019. https://clinicaltrials.gov/ct2/show/NCT02673619.

[220] "Pharmacokinetic, Safety, Tolerability, and Clinical Effect of Topical Umeclidinium in Primary Axillary Hyperhidrosis." ClinicalTrials.gov. Accessed October 2019. https://clinicaltrials.gov/ct2/show/NCT02563899.

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Epidermolysis Bullosa

Epidermolysis bullosa (EB) is a group of genetic conditions that cause the skin to be very fragile and to blister easily. Blisters and skin erosions form in response to minor injury or friction, such as rubbing or scratching. Epidermolysis bullosa simplex (EBS) and dystrophic EB are the major forms of EB. A number of clinical studies are listed in clinicaltrials.gov, but currently, there are no approved EB-specific medications. Treatment is generally focused on skin care to control symptoms and prevent infection.

Diacerein (prodrug of rhein) and rhein have been shown to inhibit the *in vitro* and *in vivo* production and activity of interleukin-1β (IL-1β) and other pro-inflammatory cytokines.[221] Diacerein 1% ointment is currently being evaluated internationally for safety and efficacy in patients 4 years and older, with a treatment duration of 8 weeks, a follow-up period of 8 weeks, and randomization stratified by genotype (KRT5 and/or KRT14 versus other genotypes).[222] The primary objective is to compare the efficacy of diacerein 1% ointment to reduce the BSA of EBS lesions being treated. In a long-term safety study,[223] treatment cycles consist of 8 weeks on treatment (once daily application) followed by 8 weeks off treatment, with use of a bland, non-medicated emollient/moisturizer, sunscreens, and routine cleansing. Inclusion criteria included a documented genetic mutation consistent with EBS. Diacerein does not correct the underlying genetic defects associated with EBS; however, it does appear to potentially improve the quality of life in affected patients. Diacerein was granted US FDA Rare Pediatric Disease designation in May 2018 and Fast Track development designation in August 2018.[217]

Trials with gene therapy for EB show potential to correct the molecular and clinical phenotype of patients with EB. Various strategies are being

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[221] Limmer, Allison L., Crystal E. Nwannunu, Radhika Shah, Kendall Coleman, Ravi R. Patel, Uyen Ngoc Mui, and Stephen K. Tyring. "Topical Diacerein Ointment for Epidermolysis Bullosa Simplex: A Review." *Skin Therapy Letter* 24, no. 3 (2019): 7–9.

[222] "Safety and Efficacy of Diacerein 1% Ointment Topical Formulation Compared to Placebo for Subjects with Epidermolysis Bullosa Simplex (EBS)." ClinicalTrials.Gov. Accessed October 2019. https://clinicaltrials.gov/ct2/show/NCT03154333.

[223] "Long Term Open-Label Study Evaluating Safety of Diacerein 1% Ointment Topical Formulation in Subjects with Epidermolysis Bullosa Simplex." ClinicalTrials.Gov. Accessed October 2019. https://clinicaltrials.gov/ct2/show/NCT03389308.

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used, depending on the type of EB and the nature of mutation inheritance, from functional gene replacement therapy based on viral expression to genome editing methods by programmable synthetic nucleases.[224] Improved delivery and limiting immune reactions are challenges for further therapeutic development.[225] Two new *in vivo* topical COL7A1 gene therapies for recessive dystrophic EB recently began early-phase clinical trials.[226,227] It will be exciting to see how emerging gene therapies will change the lives of patients with genetic disorders and stimulate innovation in the operation of clinical trials.

The FDA recently issued a Guidance for Industry regarding drug development for EB.[228] In the guidance, FDA strongly encourages sponsors to discuss with the appropriate review division in early planning stages. It is likely that the FDA takes a flexible and tailored approach for the drug development due to rarity and heterogeneity of the disease.[229] A single adequate and well-controlled trial with confirmatory evidence may suffice for approval. Trial endpoints may include effects on patients' signs or symptoms such as itching, pain, blister prevention, and wound healing, PROs and observer-reported outcomes instruments play an important role to assess the effectiveness, but there is no established or standardized measure. Sponsors should incorporate patient and caregiver perspectives in efficacy endpoint development. Due to the heterogeneity, each subtype may

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[224] Beylin, AK., NG. Gurskaya, and EA. Vorotelyak. "Methods of Gene Therapy for Treatment of Inherited Epidermolysis Bullosa." *Moscow University Biological Sciences Bulletin* 73, no. 4 (October 1, 2018): 191–98. https://doi.org/10.3103/S0096392518040016.

[225] Marinkovich, M. Peter, and Jean Y. Tang. "Gene Therapy for Epidermolysis Bullosa." *The Journal of Investigative Dermatology* 139, no. 6 (June 2019): 1221–26. https://doi.org/10.1016/j.jid.2018.11.036.

[226] Wings Therapeutics Inc. "Topical QR-313 in Recessive Dystrophic Epidermolysis Bullosa (RDEB) Due to Mutation(s) in Exon 73 of the COL7A1gene." ClinicalTrials.Gov. Accessed December 14, 2019. https://clinicaltrials.gov/ct2/show/NCT03605069.

[227] "Topical Bercolagene Telserpavec (KB103) Gene Therapy to Restore Functional Collagen VII for the Treatment of Dystrophic Epidermolysis Bullosa." ClinicalTrials.Gov." Accessed October 2019. https://clinicaltrials.gov/ct2/show/NCT03536143.

[228] Food and Drug Administration. *Epidermolysis Bullosa: Developing Drugs for Treatment of Cutaneous Manifestations*. Guidance for Industry. June 2019. https://www.fda.gov/media/128419/download.

[229] Food and Drug Administration. *Rare Diseases: Common Issues in Drug Development*. Guidance for Industry (Draft). February 2019. https://www.fda.gov/media/120091/download.

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need to have different PROs and observer-reported outcomes. Therefore, as the FDA suggested, it is critical for the sponsors to meet and discuss the development program with the FDA and obtain agreement. It is also noteworthy that the FDA suggests allowing telemedicine and mobile technology in the clinical trials to minimize visits to trial sites and maximize patient comfort and convenience. Examples include electronic informed consent, telemedicine interactions with the assistance of mobile nurses, and photographic or video documentation of wounds during routine dressing changes in the home and at specified study visits for wound observation endpoint data. To enable these technologies, the sponsor needs to discuss validation and the use of electronic PRO instruments and electronic diaries. Although these processes may be cumbersome, this is a step forward to a new era of clinical trials in the digital world.

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CHAPTER 7

CLOSING REMARKS

Dermatological drug development, whether for a new chemical entity, a repurposed compound, a reformulation, or a generic compound, may be complex; however, the pathway to success follows a negotiated development plan. The nonclinical approach for dermatological drug products is more involved than the standard approach for oral compounds that are supported by established guidelines. Challenges exist, given the requirements for additional dermal studies, the use of the minipig as the non-rodent species, increased drug supply, an evolving scientific field, and uncertainty around agency expectations. Although different from traditional drug development, phase 1, phase 2 and phase 3 studies are conducted to generate the necessary data to populate a product label and inform dosing of the final product.

The authors met and talked about a textbook to facilitate dermatological drug development in late 2018. We had previously worked together in the dermatology division of GlaxoSmithKline (GSK) until 2015. After all of us had departed GSK by 2017, we once again found an opportunity to collaborate for dermatological drug development. As many new dermatological drugs in the pipeline emerge, we thought it may be helpful for other researchers starting work in dermatological drug development field if we presented our combined lessons learned over the years into a consolidated textbook. There is no single guidance that makes every drug development project successful, but we hope the lessons we have learned, examples, and our thought process for dermatological drug development will ease the path forward for others in the field.

The need for internationally harmonized guidelines specific to dermatological drug development is apparent, and initiatives to develop these guidelines are becoming an ever-increasing demand.

While we are writing this book, dermatological drug development is advancing to the next stages. The authors sincerely hope that pharmaceutical companies, regulatory authorities, and patients will all collaborate to fill in the gaps of unmet medical needs in the dermatology field.

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Drug approval is a mission.

Patients are waiting.

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