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By

Tomoko Maeda-Chubachi,
Elizabeth Kernodle Hussey
and Sylvia Furst

Cambridge
Scholars
Publishing

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This book first published 2020

Cambridge Scholars Publishing

Lady Stephenson Library, Newcastle upon Tyne, NE6 2PA, UK

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN (10): 1-5275-5818-5
ISBN (13): 978-1-5275-5818-2

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

TABLE OF CONTENTS

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.

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

dermatological drug development and support future clinical innovation in dermatology.

It is a great time to be in dermatology!

ACKNOWLEDGEMENTS

The authors would like to thank the following people for their contributions to the creation of this book:

It was impossible to publish this book without editorial support from Stacy Jasper, our friend and colleague, who has been an excellent and skillful medical writer with many dermatological drug development experiences from the pre-IND stage through NDA and MAA approvals.

This book would not have been possible without support from our families and friends. Tomoko's husband, Takayuki, has always been supportive of her professional, as well as her personal life. His passion for cooking gave great joy to busy and often stressful days and kept her healthy with her favorite Japanese meals. His dedicated work in the backyard produced colorful views of vegetables and plants, which always provided relaxed moments when Tomoko had a brief look out of the windows.

Prof. Barbara Gilchrest, Tomoko's mentor since 1995, encouraged her to contribute to dermatology from various angles. Elizabeth Messersmith, our friend and collaborator at Novan Inc., always offered warm encouragement and navigation. Prof. Peter van de Kerkhof provided critical reviews and helpful suggestions.

Sylvia would like to express her sincere gratitude to her co-authors for providing her with the opportunity to embark on this project, and to her colleagues at Integrated Nonclinical Development Solutions for all their guidance and encouragement throughout the year in carrying out this endeavor. She is deeply indebted to her family and friends for all their moral support, cooperation, understanding, and patience, without which this work would not have been possible.

Elizabeth (Betty) would like to thank her colleagues and co-authors for their guidance, critical reviews and collaborations, along with her family, including the furry ones, for their support and patience.

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

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.

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.

Figure 1-1: Early Stage Discovery Overview

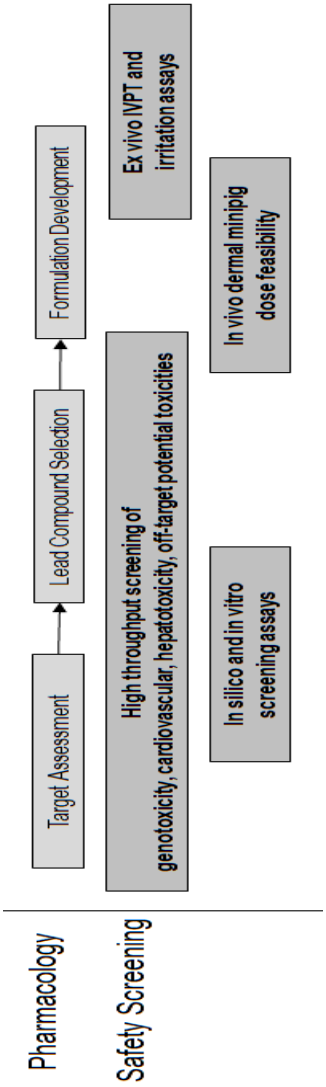
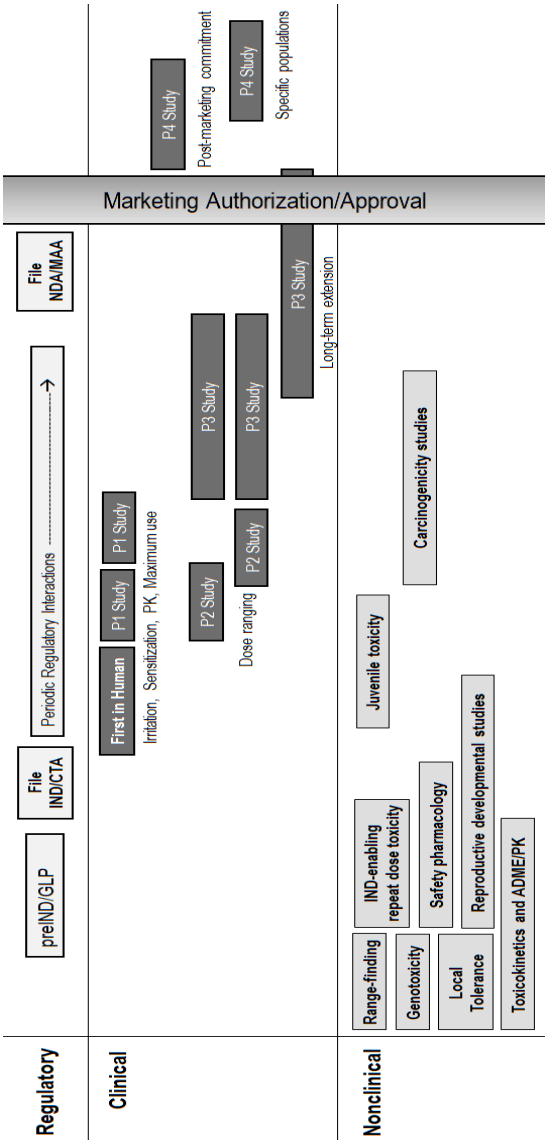


Figure 1-2: Dermatological Drug Development Overview



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.

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.

(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.

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.

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.

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.

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)).

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

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.

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

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