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Topical Development's Crystal Ball

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"Even after 3 decades, this elegant diffusion cell is still regarded as the single most powerful in vitro model for advancing dermatologic and transdermal product development. Its ability to accurately predict a drug's topical delivery and pharmacokinetics underpins numerous key product development decisions, mitigates costly failures, and accelerates navigation throughout development."

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30th Anniversary of the Franz Cell Finite Dose Model: The Crystal Ball of Topical Drug Development

By: Sam Raney, PhD; Paul Lehman, MSc; and Thomas Franz, MD

ABSTRACT

This article commemorates the 30th Anniversary of the Franz Cell and the in vitro Finite Dose Model, which revolutionized strategic drug development for topical formulations.[1,2] Even after 3 decades, this elegant diffusion cell is still regarded as the single most powerful in vitro model for advancing dermatologic and transdermal product development. Its ability to accurately predict a drug's topical delivery and pharmacokinetics underpins numerous key product development decisions, mitigates costly failures, and accelerates navigation throughout development. Its enormous impact has been not only as a key strategic asset for drug developers, but ultimately, in helping to ensure that safe and optimally effective medications have become available to patients.

INTRODUCTION

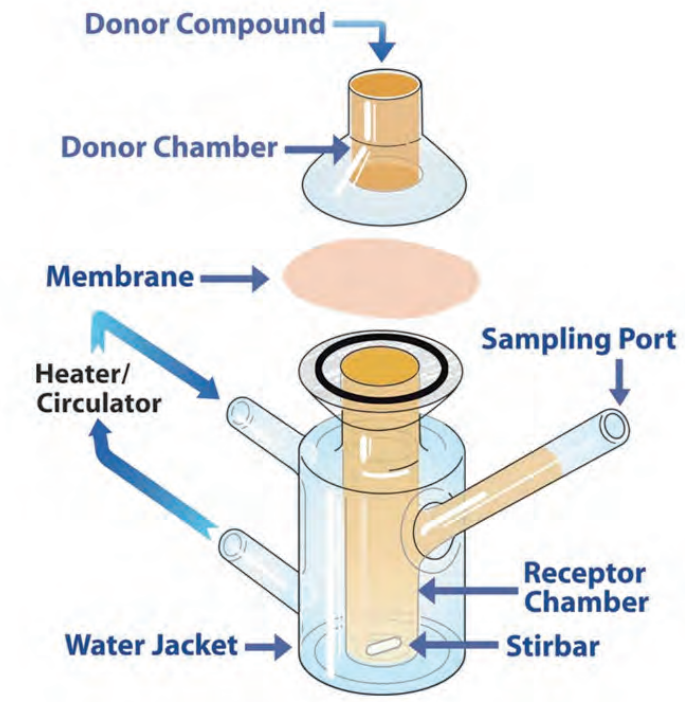
Topicals & Transdermals

Topicals and transdermals are multi-billion dollar drug delivery technologies widely utilized throughout the world. These terms refer to dosage forms administered onto the skin, but the intended site of action for topicals is the skin itself, whereas the site of action for transdermal drugs is systemic. It is expedient to refer to both collectively as topicals, and these include creams, lotions, gels, ointments, foams, shampoos, solutions, lacquers, patches, and several other novel technologies, including medical devices. Topical formulations are convenient and familiar for users, but can be extremely challenging to develop for delivering drugs effectively across the formidable skin barrier.

The Skin Barrier

The outermost layer of the skin is called the stratum corneum (SC). The impressive barrier function of skin resides primarily in this very thin, dead outer layer. The SC is composed of non-viable cells called corneocytes, and its structure and composition have evolved to form an extremely durable and effective barrier for keeping water in, and concurrently, keeping exogenous substances out. Fortunately for drug developers, because the barrier function of skin resides in this non-viable layer, and because the properties of the SC are retained when removed from the body, the absorption of topical compounds

FIGURE 1



The Components of the Franz Cell Set-up

Skin is mounted atop the base of the Franz Cell and bathed from beneath by a physiological solution within the Receptor Chamber, which is maintained at physiological temperature by a Water Jacket connected to an external Circulating Water Bath. A magnetic stirrer below the Franz Cell rotates a miniature Stir bar keeping it well-mixed. The skin is clamped between the base and an upper Donor Chamber, typically with an O-ring seal. The dose is administered from above onto the skin surface. At selected time points, the Receptor Chamber solution is collected from the Sampling Port (and the volume replaced) to measure the amount of drug that has penetrated through the skin. Following the final sampling time point, the skin can be surface-washed and recovered to evaluate drug content in the SC, epidermis, and dermis, thereby to determine distribution of the compound within the skin as well as to calculate mass balance accountability of the dose. (Adapted from an image courtesy of PermeGear – www.PermeGear.com)

through the skin barrier can be accurately evaluated in vitro, by using human skin mounted on a Franz Diffusion Cell.

Delivering Compounds Through Skin

Designing formulations to deliver drugs effectively through the skin is as much an art as a science. It is surprisingly difficult to anticipate the impact of alterations in formulation design on dermal absorption of the drug. Neither animal models nor mathematical simulations are consistent, or accurate, at predicting either dermal absorption or product performance in humans. There are numerous physicochemical characteristics of the penetrating compound, combined with significant contribution of the formulation matrix, that together influence absorption of the compound through human skin. Ultimately, this absorption can only be accurately predicted when evaluated using human skin.

THE FRANZ CELL FINITE DOSE MODEL

Franz & Lehman – The Men Behind the Model

The Franz Cell Finite Dose Model utilizes human skin obtained from surgical procedures or organ donors. The skin is mounted onto glass chambers called Franz Diffusion Cells (Figure 1), so named for Thomas J. Franz, MD. During a scientific partnership spanning 3 decades, Dr. Franz and Paul Lehman innovated many of the key methodologies for utilizing the Franz Diffusion Cell to accurately model clinical situations for the dermal absorption of drugs.

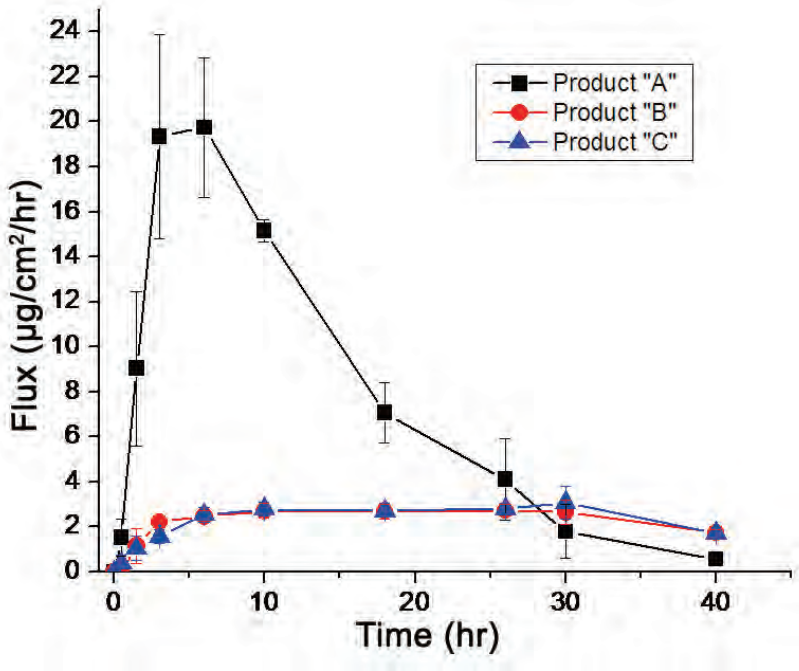
Adaptations & Variations of the Design

The fundamental design of the static Franz Cell is widely accepted and remains the most popular and versatile diffusion cell design. In addition, several adaptations have been made to the basic design. Some examples include the Bronaugh Cell, which has a flow-through reservoir compartment, the Hanson Cell, which is designed as part of an automated sampling system, and a modified Franz Cell, which is adapted for toe and finger nails.[3,4]

The Finite Dose Model & Predictive Modeling

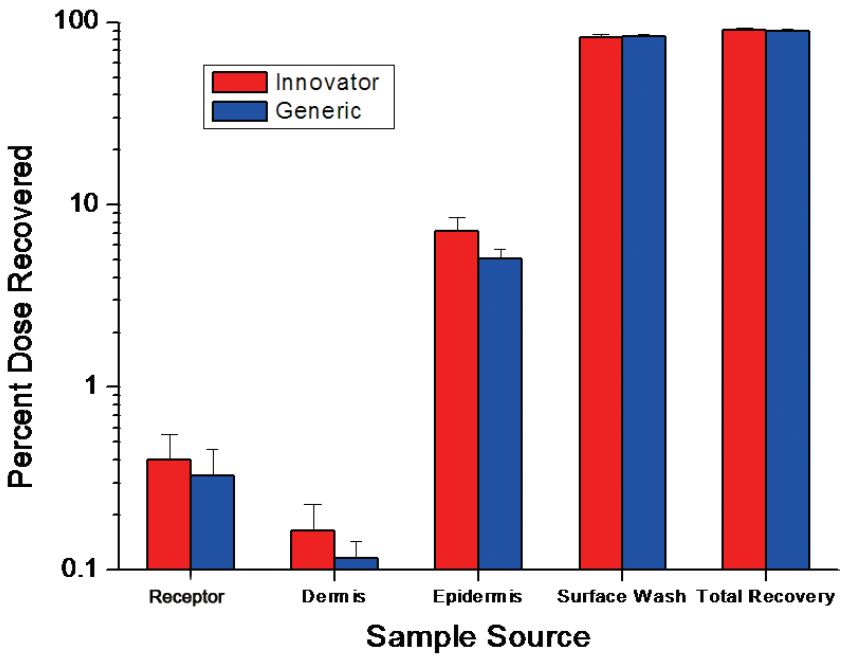
The Franz Cell provided the foundation for in vitro percutaneous absorption studies. However, beyond the cell or any of its adaptations, it was necessary to develop

FIGURE 2



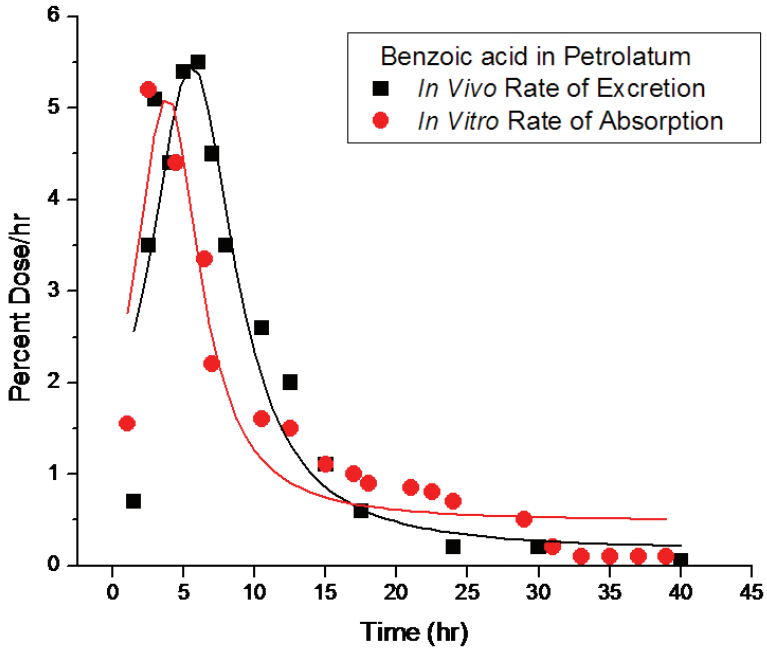
Predicting Product Performance Among Prototypes
This figure demonstrates typical absorption profiles of a single drug in three different formulations. The time course of absorption is characterized by the Flux (rate of absorption) of the compound across the skin as a function of Time, which also shows the total amount absorbed, as the area under the curve. This is utilized to evaluate equivalent performance of generics and innovators or to evaluate significantly different performance among comparator formulations.

FIGURE 3



Dermal Distribution & Mass Balance Accountability
When dose mass balance studies are conducted, residual surface dose, and the distributed content within the epidermis and dermis can also be determined.

FIGURE 4



In Vitro - In Vivo Correlation
The rate of absorption of topically administered Benzoic Acid measured in vitro correlates precisely with the rate of excretion measured in vivo. This is one of many different ways in which the agreement between in vitro and in vivo data has been demonstrated.

insightful methodologies to accurately model the clinical situation. One of the most important examples of this was the Finite Dose technique; the use of a clinically relevant finite dose administered to the skin (~ 3 to 5 mg/cm^2).[2] This new methodology was essential to accurately model the clinical scenario, and was a critical step forward from the prior practice of using an infinite dose to evaluate the percutaneous absorption of topical formulations. An infinite dose can artificially alter the skin barrier, leading to an elevated rate of absorption of the drug across the skin, and an artificial representation of steady state kinetics. By contrast, a finite dose accurately models the pharmacokinetic rise to a maximum peak rate of absorption, followed by a declination phase as the applied surface dose becomes depleted of drug (Figure 2).

Measuring Rate of Release & Skin Metabolism

Other investigators have added to the wealth of knowledge that can be obtained from the Finite Dose Model. One particularly noteworthy example is the use of freshly excised surgical skin, in which metabolic activity can be maintained and from which drug metabolism can be assessed during its percutaneous absorption.[5] Another example is the use of inert membranes to assess the rate of release of drug from the vehicle matrix.[6] The latter instance, using the FDA SUPAC-SS Guidance for semi-solid dosage forms, is commonly utilized throughout stages of topical formulation development to evaluate alterations in the vehicle matrix, which may change the equivalent rates of release among batches.[6]

THE CRYSTAL BALL: IN VITRO - IN VIVO CORRELATION

Building a Topical Product

There are numerous common variables that tend to impact the performance of topical formulations throughout development. The in vitro Franz Cell Finite Dose Model has played a central role facilitating both the efficiency and sophistication of modern topical drug development by providing an accurate and predictive in vitro tool to assess clinical bioavailability and bioequivalence. Topical drug development involves a process of selecting the compound or analogue with the best inherent absorption characteristics through human skin, selecting the most appropriate topical formulation type (cream, gel, etc), selecting the optimum formulation composition, as well as selecting the appropriate concentration of the active ingredient in the formulation, all to ultimately achieve the desired magnitude, profile, and duration of dermal absorption.

Delivery of the compound into the skin can also be very sensitive to changes in the formulation matrix. These include changing sources of the excipients or actives, as well as scale-up, changes in manufacturing processes, changes in manufacturing sites, or even inherent lot-to-lot variability. Consistency in product performance throughout development is essential to compare data across the successive stages, and is particularly important before utilizing a batch in multi-million dollar clinical trials. Similarly, during the process of generic product development, it is essential to engineer formulations from which the absorption of the active(s) through human skin is equivalent to the innovator in magnitude, profile, and duration.

Predicting Drug Delivery for Pharmaceuticals

Percutaneous absorption represents the A in ADME (Absorption - Distribution - Metabolism - Excretion), and it has been consistently demonstrated that in properly modeled and well-conceived studies, which are conducted under identical conditions (matched dose, body site, duration, etc), the in vitro results correlate with and predict in vivo results (Figure 4). Using basic pharmacokinetic principles, this input-function (the absorption phase) thereafter allows for prediction of systemic blood levels, particularly if the clearance and excretion have been well characterized for the drug of interest.[7] Experienced implementation of this model has shown it to be the single best surrogate model for the assessment of bioavailability and bioequivalence for topically administered compounds. As such, because of its predictive power, the model has become the gold standard used by experienced pharmaceutical, biotech, and specialty companies (Figure 5).

When using the Franz Cell and the Finite Dose Model for predicting in vivo bioavailability and percutaneous absorption pharmacokinetics, one must be cognizant of the following three key criteria to ensure success:

1. Be consistent in study design between the in vitro and in vivo methods (eg, same dose amounts, formulations, exposure durations, target body site, etc);

2. Be fully trained in the use of the Franz Cell and the Finite Dose Model; and

3. Have a complete understanding of the penetrant's chemical characteristics in

relation to skin physiology, formulation design, and the diffusion process.

Predicting Systemic Risk Via Dermal Absorption for Toxicology

In addition to predicting drug delivery for pharmaceuticals, this model is also used to assess the potential systemic exposure from toxic compounds that may come in contact with human skin, such as pesticides and herbicides. This approach is particularly valuable for manufacturers of cosmetic excipients and industrial chemicals, and for government agencies needing to evaluate dermal exposure and toxicity, while minimizing the use of live animal research.

Predicting Equivalent Dermal Absorption for Generics

Another common application of the in vitro Franz Cell Finite Dose Model using human skin is during the development of generic topical products. Given the recognized difficulty to exactly match the manufacturing processes of an innovator, multiple variations of generic formulations can be tested in vitro to determine which one most closely matches the innovator (Figure 2). Clinical trials are the basis for approval of most generic topicals, so it is critical to confirm equivalent product performance between test and reference lots prior to conducting the pivotal clinical dermatology bioequivalence study. Demonstrating equivalent rate and extent of absorption in vitro using the Franz Cell provides a high degree of assurance that bioequivalence will be demonstrated in the clinical trial, where the consequences of failure in a clinical study are dire.

REVOLUTIONIZING DECISION-MAKING THROUGHOUT TOPICAL DEVELOPMENT

The in vitro Franz Cell Finite Dose Model has revolutionized topical product development throughout the past 30 years, and has served as a powerful and sensitive tool by which to accurately quantitate a drug's rate of percutaneous absorption. This in vitro model has become much more than simply a preclinical tool and has grown to be utilized within multiple stages of the drug development process. Preclinically, it is used principally to screen and select the optimum formulation for further development. However, as data continually emerges into the public domain supporting the validity of the model as a surrogate for in vivo measurements of bioavailability and bioequivalence, its application within other phases of the drug development process have become increasingly evident, including the following:

- Evaluating reformulation changes during Phases I-III;
- Development of line extensions and products with altered or enhanced delivery;
- Scale-up changes; and
- Post-approval manufacturing changes

FIGURE 5

Franz Cell Studies are a standard part of development for topicals and transdermals, from preclinical candidate screening and formulation optimization to evaluation of manufacturing specifications and lot-to-lot comparison, as well as for verification of clinical batch performance and equivalence, prior to multi-million dollar clinical trials.

THE FUTURE

Harmonization of Percutaneous Absorption Testing

International initiatives are currently underway to harmonize and standardize the methodologies for conducting studies with the in vitro Franz Cell Finite Dose Model. This standardization will facilitate the comparison of datasets across laboratories and within the literature. This, in turn, will be important to support greater utility by regulatory agencies.

Artificially Cultured Human Skin

The barrier properties of cultured skin models are currently inadequate for absorption studies, and they tend to over-predict absorption. But if they are eventually able to develop a normal SC and competent barrier function, they will be of particular value with Franz Cells in countries where moral or cultural roadblocks preclude the use of natural human skin. Currently, their value is limited to modeling such things as metabolism or cellular responses to penetrating drugs or chemicals.

Substituting Live Animal Research

European initiatives are currently shifting product development paradigms away from in vivo live animal models. Furthermore, the absorption of topically applied compounds in vivo is often at very low levels, and then become even further diluted when monitoring the drug in blood. Sensitive modern analytical techniques, such as LC/MS and LC/MS/MS, or even ligand binding assays, in combination with the in vitro Franz Cell Finite Dose Model, provides an ideal way to provide optimal sensitivity for characterizing percutaneous absorption. Also, in concert with the science, improved documentation and QC/QA oversight as a standard part of these studies is imperative to ensure confidence in the objective quality of the results. In the foreseeable future, data from the in vitro Franz Cell Finite Dose Model could become a part of the basis for approval by international regulatory bodies, as a replacement for more costly, more time consuming, and poorly predictive animal tests.

Franz & Lehman - The Future Happens With Each New Day

Tom Franz, MD, and Paul Lehman, MSc, have worked together for 3 decades, within academia, at the FDA, as consultants, and now, within a contract research organization, to advance the science and practical methodologies for topical product development. Their laboratory started at the University of Washington in Seattle with a handful of cells and a few small experiments each month. Now, as part of the Cetero Research facility in Fargo, North Dakota, they evaluate several thousand skin sections each year with sophisticated analytical capabilities for radiolabel and LC/UV/MS methods, and with industry-standard quality control and quality assurance infrastructure. Throughout the years, they have continually innovated new methodologies for novel situations, collaborated with other experts in the field, contributed to industrial consortium projects, and systematically advanced the development of a large portion of the topical compounds currently on the pharmacy shelves. In addition to conducting both in vivo and in vitro contract work for the industry, they continue to perform independent research to further refine and advance the Franz Cell Finite Dose Model, contribute to national and international symposia, and maintain active dialogue with regulatory agencies related to topical pharmacokinetics.

The Franz Cell has not only survived the test of time, it continues to prove its value to the industry for product development, predicting bioavailability and bioequivalence, and assessing systemic risk for potential toxins. No other model has been developed that can provide so much valuable in vitro information as this simple, but elegant, glass chamber. Throughout the past 30 years, the Franz Cell has become the crystal ball used by topical and transdermal developers to navigate and streamline their critical paths for drug development, and the coming decades will likely see even more utility for this model in topical drug development.

For more information or to contact the authors, please e-mail FranzCell@Cetero.com or call 701-356-2480.

REFERENCES

1. Franz TJ. Percutaneous absorption: on the relevance of in vitro data. J Investigative Dermatol. 1975;64:190-195.
2. Franz TJ. The finite dose technique as a valid in vitro model for the study of percutaneous absorption in man. In: Simon B, Paster Z, Klingberg M, Kaye M, eds. Skin: Drug Application and Evaluation of Environmental Hazards, Current Problems in Dermatology. Vol. 7. Basel, Switzerland: Karger Press. 1978;58-68.
3. Bronaugh RL, Stewart RF. Methods for in vitro percutaneous absorption studies IV: the flow-through diffusion cell. J Pharmaceut Sci. 1985;74(1):64-67.
4. Hanson Research. The vertical diffusion cell. Website: www.hansonresearch.com. 2000.
5. Collier SW, Sheikh NM, Sakr A, Lichtin JL, Stewart RF, Bronaugh RL. Maintenance of skin viability during in vitro percutaneous absorption/metabolism studies. Toxicol Applied Pharmacol. 1989;99:522-533.
6. US Department of Health and Human Services – Food and Drug Administration – Center for Drug Evaluation and Research, SUPAC SS Guidance for Industry – Nonsterile Semi-solid Dosage Forms – Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation. Website: www.fda.gov/cder/guidance/1447fnl.pdf. May 1997.
7. Wagner JG. Pharmacokinetic absorption plots from oral data alone or oral/intravenous data and an exact Loo-Riegelman equation. J Pharmaceut Sci. 1983;72:838-842.

BIOGRAPHIES

Dr. Sam Raney is the Associate Director of Pre-Clinical Dermatology at Cetero Research. He has over 15 years of experience in skin research and drug development. He is an authority on regulatory aspects, including FDA, EPA, and OECD GLP, as well as International Guidelines pertaining to the conduct of in vitro percutaneous absorption studies. His experience as an industrial scientist, a topical drug development consultant, and a scientific due diligence analyst encompasses strategic pharmaceutical candidate development, scale-up and manufacturing, intellectual property development, and management of drug development projects. Dr. Raney earned his BA in Molecular Biophysics & Biochemistry from Yale University, his MSc in Biology from Marshall University, and his PhD in Biochemistry & Molecular Biology from the University of British Columbia (UBC) in Canada. He was a Research Fellow within the UBC Faculty of Medicine, Division of Dermatology, conducting research in skin barrier function, model membrane systems, barrier replacement therapy, and skin barrier protection technologies for the Department of Defense. Dr. Raney's research has included work in skin tissue regeneration for burn patients, and the development of vaccines and adjuvants using liposomal formulations. His credentials include several each of manuscript publications, poster and lecture presentations, copyrights, and patents.

Mr. Paul Lehman is the Director of the Clinical & Pre-Clinical Dermatology at Cetero Research. He has conducted internationally recognized research in the field of topical pharmacokinetics and topical bioequivalence for 30 years. He earned his BA in Biology, and BBA from Incarnate Word College in San Antonio, Texas. Mr. Lehman later earned his MS in Pharmaceutics at the University of Washington in Seattle. His prior appointment was as Executive Vice President of Clinical and Pre-Clinical Dermatology at DermTech International in San Diego, California. Mr. Lehman has also held faculty appointments at both the University of Arkansas for Medical Sciences and at the University of Washington. In addition, he worked for 2 years at the National Center for Toxicological Research (FDA) in Jefferson, Arkansas, and is currently an Adjunct Professor at North Dakota State University in Fargo. Mr. Lehman has been an integral partner with Dr. Thomas Franz in the conduct of in vitro and in vivo topical pharmacokinetics and the development and validation of dermato-pharmacokinetic bioequivalence methods for topical formulations.

Dr. Thomas Franz is the Executive Medical Director of Clinical Dermatology at Cetero Research. He has over 30 years of academic and industry experience in dermatologic research. Dr. Franz earned his BS from the University of Portland, his MS in Biochemistry, and his MD from the University of Oregon Medical School. His prior appointments include Consulting Medical Officer at the FDA's Division of Topical Drug Products at the Center for Drug Evaluation and Research (CDER), Professor at the Department of Dermatology, University of Arkansas for Medical Sciences, and Associate Professor, Department of Medicine, Division of Dermatology at the University of Washington School of Medicine. Dr. Franz was previously Vice President, Clinical Research in Dermatology at Connetics Corporation, Vice President, Research and Development at Hercon Laboratories, and held management positions at Hoffmann LaRoche, Johnson & Johnson, and Procter and Gamble.