PharmaED RESOURCES, Inc.

Transdermal & Intradermal Drug Delivery Systems 2017

Advanced Design, Development & Delivery of Skin-Mediated Therapies and Vaccines

September 28–29, 2017, Racquet Club of Philadelphia, PA

Featured Speakers Include:

Thean Yeoh
Pfizer

Bobby Singh
Corium

Lisa Dick
3M

Mikolaj Milewski
Merck

Samir Mitragotri
UC Santa Barbara

Ryan Donnelly
Queens University

With Comprehensive Coverage On:

- Improving Bioavailability Via Transdermal Administration
- Latest Advances in Microneedle Drug and Vaccine Delivery
- How to Move from Passive to Active Skin-Mediated Delivery Technologies for Drugs and Biologics
- Optimizing TDD & IDD for Efficacious Delivery and Patient Compliance
- Computational Modeling of Transdermal and Intradermal Delivery
- Resolving Regulatory Compliance Issues for TDD & IDD Systems
- Mechanisms of Dermal and Transdermal Absorption of Drugs
- IVPT and IVRT of Transdermal and Topical Products
- Exploring the Promise of Ionic Liquids for Transdermal Applications
- And much more!

The growing interest in alternative routes of drug administration has experts predicting that the market for transdermal and intradermal drug delivery systems will exceed $25 billion in 2018. The industry is on the threshold of bringing into commercial production a new generation of transformative TDD and IDD therapies and delivery systems. That is why you cannot afford to miss this two-day intensive conference. Pharma Ed brings together leading researchers in the field to share the most recent advances in the design, formulation, and delivery of skin-mediated therapies and vaccines.

With Representation From:

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Thursday, September 28, 2017

7:45 *Complimentary Breakfast & Chairperson's Welcome and Opening Remarks*

The Transdermal & Intradermal Landscape—Key Challenges and Opportunities

8:15 **How Challenges Evolve for Delivery into Skin as we Transition from Passive Diffusion to Delivery Technologies**

Dr. Ajay Banga, Chair & Professor of Pharmaceutical Sciences, Mercer University

Moderately lipophilic drugs can passively diffuse into skin but even these simple patches are considered to be drug-device combinations and face challenges such as drug crystallization, cold flow, or failure of adhesive. Hydrophilic molecules and macromolecules do not normally pass through the skin unless enabling technologies are used, and these offer different types of challenges. For example, iontophoresis is limited to deliver molecules up to around 13kDa and may potentially induce skin burns if skin contact is not uniform. Sonophoresis and laser-based devices may face challenges to miniaturize the device for home use by patients. Innovations and challenges in these technologies, especially for iontophoresis, ablative and non-ablative fractional laser, and microneedle-based devices, will be presented.

- Learn about challenges facing passive patch development, e.g., drug crystallization and how these challenges change as we move into delivery technologies, e.g., potential burns with an iontophoretic patch.
- Learn how new technologies are expanding the scope of transdermal delivery to include hydrophilic macromolecules
- Learn the success and failures of novel skin delivery technologies developed and marketed over the years.

8:55 **Keynote: Recent Advancements in Intradermal Delivery of Biopharmaceuticals**

KEY NOTE

Lisa Dick, Ph.D., Lab Manager & Technology Leader, 3M Drug Delivery Systems

As population demographics shift and new medicines become available, patient preferences and new technologies remain top of mind at 3M. In recent years, 3M has been developing a patient-friendly and easy-to-use microstructured transdermal system drug delivery platform that includes solid and hollow microneedle options along with associated applicators. These devices are well suited for dermal skin targets or systemic distribution for drugs that enter the lymphatic system. This talk will include recently generated data and examples that support intradermal delivery as a method to meet the evolving needs of pharmaceutical companies, regulators, providers, and patients.

9:35 **Streamlined 505(b)(2) Transdermal Development Pathway for Potentially Faster Commercialization**

Bobby Singh, Ph.D., Chief Technology Officer, Corium International

Abstract Coming Soon

10:15 *Networking Coffee Break*

Critical Issues—The Pharmacokinetics of Transdermal Delivery

10:40 **Minimization of CYP2D6 Polymorphic Differences and Improved Bioavailability via Transdermal Administration**

Thean Yeoh, Ph.D., Associate Research Fellow, Pfizer

Transdermal delivery has the potential to offer improved bioavailability by circumventing first-pass gut and hepatic metabolism. This presentation will describe pharmacokinetic differences between transdermal and oral delivery of latrepirdine in extensive and poor CYP2D6 metabolizers (EM/PM). Dose-normalized latrepirdine total exposures were approximately 11-fold and 1.5-fold higher in EMs and PMs, respectively following administration of transdermal relative to oral. Differences between EM and PM latrepirdine exposures were decreased, with PMs having 1.9- and 2.7-fold higher peak and total exposures, respectively, following transdermal administration compared to 11- and 20-fold higher exposures, respectively, following oral administration. Transdermal delivery can potentially mitigate the large intersubject differences observed with compounds metabolized primarily by CYP2D6. Transdermal delivery was readily accomplished in this early clinic evaluation using an extemporaneously prepared solution.

Spotlight on Microneedle Arrays—The Present & (Near) Future of Microneedle Drug Delivery

11:20 **How Microneedle Arrays Can Overcome the Challenges Facing Transdermal Drug Delivery**

Dr. Ryan F. Donnelly, Chair in Pharmaceutical Technology, Queen's University Belfast

Transdermal delivery using conventional passive patches has perhaps passed its peak. Second generation physical enhancement techniques, such as ultrasound and iontophoresis have not progressed as once hoped. Research based upon microneedle arrays has intensified recently. While the initial focus was on biomolecules, the field has expanded to include delivery of conventional small molecule drugs. Much success has been achieved, particularly in the vaccines field. Recent innovations have focused on enhanced formulation design, allowing delivery of clinically relevant doses of small molecule

drugs and biomolecules, larger patch sizes and scalable manufacture. However, no true microneedle-based drug delivery system has yet been marketed. A number of regulatory and manufacturability queries have been raised and those in the field are now actively working to address them. Microneedle-based transdermal drug delivery systems have tremendous potential to yield real benefits for patients and industry, especially if they can be shown to deliver therapeutic doses of drugs clinically, rather than simply vaccines. Through diligence, innovation and collaboration, this will begin to be realized over the next 3–5 years.

12:00 *Complimentary Networking Lunch*

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1:15 CASE STUDY

Clinical Trial Experience with the Intracutaneous Microneedle Systems: Experience in Osteoporosis, Diabetes, and Migraine

Pete Schmidt, Senior Medical Director, Zosano Pharma

Zosano has developed intracutaneous microneedle systems for parathyroid hormone, glucagon, and zolmitriptan. Previously, we reported results from a 6-month study in post-menopausal females with osteoporosis, and reversal of insulin-induced hypoglycemia in Type 1 Diabetes Mellitus subjects. Most recently, we announced results of a 589-subject placebo-controlled trial in subjects with migraine. In that trial, intracutaneously administered zolmitriptan was highly effective for the treatment of migraine, with statistical significance compared to placebo achieved for the two co-primary endpoints of pain freedom at 2 hours, and most bothersome symptom absence at 2 hours. We believe this trial will form the basis for approval, in conjunction with an ongoing long term safety study. In addition to efficacy observed in this trial, tolerability was also good, as the most common adverse events were application site reactions of short duration. Nearly all subjects in the trial were able to use the applicator and patch on an outpatient basis to administer study drug. A non-oral route of administration is particularly valuable in migraine, where speed of onset is critical for producing relief, and gastric stasis is often present, which slows the absorption of orally-administered products. Our results in three different patient populations demonstrate the utility of the intracutaneous microneedle systems for delivering drugs rapidly and producing pharmacologic effects quickly. We intend to seek registration of the zolmitriptan system in less than two years and believe it will be an important addition to the products available to treat migraine. It will also demonstrate that this route of administration has great potential for the rapid delivery of a number of therapeutic compounds.

1:55 CASE STUDY

Sustained Delivery of an HIV Subunit Vaccine Using Silk Microneedle Skin Patches Promotes Robust Immune Responses

Dr. Archana V. Boopathy, Postdoctoral Researcher, Massachusetts Inst. of Technology (Contributing Authors: Anasuya Mandal, Dan W Kulp, Sudha Kumari, Wade Wang, Nitasha R Bennett, Yanpu He Talar Tokatlian, William R Schief, Paula T Hammond, and Darrell J Irvine)

Novel immunogen design and vaccine delivery strategies are critical for the development of an effective prophylactic HIV vaccine. Recent studies in our laboratories have shown that the kinetics of vaccine exposure modulate humoral immune responses. To control release kinetics in the setting of a prophylactic HIV vaccine, we developed a dissolving microneedle patch (MN) that implants a solid polymer tip carrying antigen and adjuvant into the skin, with release kinetics dependent on MN composition. We utilized silk protein to form MN tips encapsulating an HIV envelope trimer (SOSIP) and adjuvants, supported on a poly acrylic acid (PAA) base. Upon dermal application, rapid PAA dissolution is followed by sustained release of vaccine, with release kinetics regulated by the degree of beta-sheet crystallinity in the silk. Antigenicity of SOSIP encapsulated and subsequently released from silk was maintained, as determined by binding to broadly neutralizing antibodies (bNAbs: PGT151,PGT145, PGT121 and VRC01) without binding to non-bNAb (39F, 14e, 4025 and B6). Following immunization in mice, we observed SOSIP and silk co-retention at the skin site of MN application over time. In the draining lymph nodes, MN delivery resulted in significantly higher SOSIP retention compared to intradermal injections. Further, silk MNs promoted germinal center (GC) responses in lymph nodes with significantly higher GC B cells and T follicular helper cells for at least 14 days following immunization compared to intradermal injections, and substantial increases in anti-SOSIP IgG titers. These results suggest the potential of silk MNs in modulating release kinetics of HIV subunit vaccine.

2:35

Thermostable Oxytocin-Coated Microneedle Patches

Dr. Yasmine Gomaa, Research Scientist, School of Chemical & Biomolecular Engineering, Georgia Tech (Contributing Authors: Chandana Kolluru, Mikolaj Milewski, Jingtao Zhang, Robert Saklatvala, Mark Prausnitz.)

Oxytocin (OX) is a nonapeptide hormone produced by the hypothalamus and secreted by the pituitary gland with both peripheral and central actions. Peripheral actions of OX have been known for years in promoting lactation, inducing delivery and preventing/treating postpartum hemorrhage. Central actions of oxytocin have recently attracted attention due to OX-mediated behavioral effects and its potential use in treatment of conditions such as schizophrenia and autism. OX is available as injections or nasal sprays with the need for a cold chain of storage

and transportation, which may not always be feasible, particularly in rural and tropical areas. OX-coated microneedle (MN) arrays can serve as a substitute, providing an accurate thermostable single dose of the drug in a fast-dissolving solid state form that can be administered by less-experienced health workers into the skin. To achieve this objective, several coating formulations including sugars and biopolymers were coated onto stainless steel MNs and the OX load was determined using HPLC during a storage time of up to 2 years at elevated temperatures up to 40°C and humidity levels up to 75% rh. Several screened coating formulations resulted in MN arrays with a uniform coating of the drug and good insertion into skin, as determined microscopically. The target OX dose of 10 IU was successfully coated onto 5 MNs and was released into the skin within 1 min after insertion. OX-coated MNs showed no significant loss of potency for at least two months of storage at 40°C and 75% rh. Formulations containing trehalose in a mixture of citrate buffer and ethanol retained 75% of OX potency at 40°C under desiccated conditions for 12 months, during which time the commercial OX product Pitocin® was reduced to 35% potency. These findings suggest the potential utility of MN patches to replace current OX dosage forms due to ease of use, thermostability and simplified logistics.

3:15 *Afternoon Networking & Coffee Break*

3:40 CASE STUDY

Microneedles to Treat Pain of the Temporomandibular Disorders

Dr. Harvinder Gill, Associate Professor of Chemical Engineering, Texas Tech

Temporomandibular disorders (TMDs) include conditions characterized by pain and/or dysfunction in the temporomandibular joint (TMJ) and masticatory muscles. Pain control is a major objective in the management of TMDs and is the primary reason for patients to seek treatment. In the US, an estimated 5% to 12% of the population is affected by TMDs, and about 4 billion US dollars are spent annually to manage TMDs. Presently there is lack of both an effective pharmacological agent and a delivery method for the treatment of TMD-associated pain conditions. The compound, 15-deoxy-$\Delta^{12,14}$-prostaglandin J2 (15d-PGJ2) has anti-inflammatory properties and is naturally formed in the human body, and is thus safe. We have previously shown that an intra-TMJ injection of 15d-PGJ2 in nanogram amounts can alleviate TMJ pain in a rat model. However, intra-TMJ injections are painful. We next hypothesized that instead of injections, microneedles could be used for topical delivery of 15d-PGJ2. In this study we have evaluated microneedles for transdermal delivery of 15d-PGJ2 and compared it to the intra-TMJ injection in a rat model of TMJ pain. The results of this study will be discussed to show that microneedles can offer better and longer lived treatment response as compared to intra-TMJ injections.

New Product Spotlight— MMJ Transdermal Patches

4:20

Production Considerations for Cannabis Patches

Ken J. Miller, Ph.D., ISYN Consulting LLC (Contributing Authors: NC DeMena & M Frid, Manna Molecular Sciences LLC.)

Broadened acceptance of cannabis and cannabis-derived products in the US has created an expanding market for new products including topical and transdermal patches. Unfortunately, manufacturing these products to meet demand is uniquely challenging due to the paradox of operating legally at the state level while under the blanket of nationwide prohibition. Historically, transdermal and topical patches are manufactured at grand scales in a single factory and distributed nationally or internationally. However, this model is not appropriate for cannabis-derived products because there is no mechanism for interstate commerce (even if legal in adjoining states). Currently, all cannabis and cannabinoid extracts must be sourced, distributed and utilized within a given state to avoid falling under federal jurisdiction.

While the restrictions associated with that prohibition may change, there is no telling when that might happen. In the meantime, we are pursuing a compliant manufacturing strategy combining large-scale centralized intermediate manufacturing and point-of-use finished product manufacturing to maximize quality and minimize production and distribution costs.

5:00

Considerations of Analytical Evaluation ofTransdermal Patches

Andrew Hall, PhD, Study Director, Toxikon Corporation

Abstract: New advances in drug delivery technology has allowed for topical and transdermal delivery systems to expand immensely in consumer markets. With the evolution in the various patch designs and their limitations as well as requirements for transdermal delivery. The cost of clinical studies is not only expensive and time consuming, but developing the right testing strategy is important for successful development. Choosing the right analytical methodology can have profound effects with regard to variability, safety and regulatory aspects. Understanding the guidance on analytical method selection for development and quality control with respect to dose analysis, elemental impurities, degradation, stability testing, bioavailability, and the challenges of dissolution testing during the drug product development and life cycle is critical to success.

5:30 *End of Day One*

Friday, September 29, 2017

7:30 *Complimentary Breakfast*

7:45 *Chairperson's Opening Remarks*

8:00 **The Advances in Bioequivalence Assessment of Generic Topical Drugs**

Theo Kapanadze, Chief Scientific Officer, Diteba

In accordance with the recently released FDA draft guidance on acyclovir, Diteba presents on a fully compliant approach that combines the extensive acyclovir *in vitro* release testing (IVRT) and *in vitro* skin permeation testing (IVPT). This approach provides drug companies with the optimal chance of biowaiver success in lieu of the high cost and long delivery times associated with human clinical trials.

Critical Issues—Assessing TD and ID Absorption

8:30 **Getting a Handle on Variability in Transdermal Absorption Assessment: In Silico, In Vitro, and In Vivo Methods**

Mikolaj Milewski, Ph.D., Associate Principal Scientist, Merck

One of the key parameters to be evaluated as part of any transdermal drug delivery feasibility assessment is the maximum flux across the skin. There is no shortage of in silico, *in vitro*, and in vivo methods that address this question. Early stages of drug development usually employ simple in silico methods with limited inputs and provide a rough maximum skin absorption rate estimate. More time-consuming experimental *in vitro* diffusion studies can provide a better measure of the percutaneous flux at later stages. Finally, in vivo studies represent an ultimate test for a transdermal product. But is it really so?

Here we will examine the variability in the estimation of maximum percutaneous flux using different predictive methods as compared to the clinical absorption rates from approved marketed transdermal drug delivery systems. The analysis will highlight the performance of 1) selected predictive equations, 2) *in vitro* transdermal permeation from saturated drug solutions, and 3) *in vitro* transdermal permeation from prototype patches; as they compare to in vivo transdermal permeation from marketed patches. As a result an appreciation will be developed for varying degree of predictive power and cautious data interpretation.

9:10 **Why Is Intradermal Absorption Faster than Subcutaneous?**

Yash Kapoor, Ph.D., Associate Principal Scientist, Merck

Delivery through the skin remains an interesting area of research though the barrier properties of the skin limit the opportunities in this drug delivery platform. Passing the transdermal barrier to deliver drug inside the dermis, technologies such as microneedles, electroporation, etc. have been introduced and explored in the past few decades. Pharmacokinetic (PK) responses through intradermal (ID) delivery can be intuitively thought to be similar to a subcutaneous (SC) delivery at first estimation but there have been many studies conducted which highlight a marked difference in delivery through these two tissues especially for larger molecules. Many past studies have highlighted the atypical pharmacokinetics response of high maximum plasma concentration and shorter time to reach the maximum concentration for ID delivery when compared to SC. Though this has been demonstrated in various studies either by direct evidence of measurements at the delivery sites or by the PK outcomes, there is limited discussion on 'why' these outcomes are the way they are. Could this be attributed only to the physiology or there are local responses during drug delivery that lead to the observed variability? And what happens when external factors such as local disease state convolute the outcomes? To discuss these questions, various resources are pooled together and a conclusive outcome is proposed. The steady state observations are limited as it is not possible to maintain steady state during experiments. Thus, it is a little difficult to independently separate some factors and understand them closely. Still, a fair assessment can be made to discern ID and SC delivery. A thorough evaluation is therefore presented to discuss these two delivery routes with a deliberate focus on developing a sound hypothesis to explain the observed PK differences.

9:50 *Networking Coffee Break Sponsored by:*

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Research Spotlight—The Promise of Ionic Liquids for Transdermal Applications

10:15 **Ionic Liquids for Transdermal and Intradermal Applications**

CASE STUDY

Dr. Samir Mitragotri, Mellichamp Chair Professor, Dept. of Chemical Engineering, UC Santa Barbara

Delivery of actives into skin for therapeutic and personal care applications is a major challenge, especially for macromolecules. Transport of molecules into skin is limited by their large size and charge. Further, some of the actives can be quite irritating to the skin and use of such actives in topical products is limited. Several approaches have been put forth to address this challenge. Our laboratory is actively exploring the use of ionic liquids as a novel formulation basis to address these challenges. Ionic liquids are liquid salts comprising pairs of cationic and anionic organic molecules. They offer several advantages for transdermal drug delivery. By selecting the appropriate cationic and anionic species, a wide range of ionic liquids can be designed. Our laboratory has demonstrated the potential of ionic liquids for various aspects of topical formulations. First, we have demonstrated that certain ionic liquids can serve as broad-spectrum antimicrobial agents and possess the

ability to penetrate bacterial biofilms. Such ionic liquids can offer novel means to treat a variety of skin conditions of infectious origin. Second, ionic liquids can serve as designer solvents for topical delivery of hydrophilic, hydrophobic, charged and macromolecular drugs. Since the ionic liquids can be tuned by selecting various anions and cations, this approach provides excellent flexibility for designing solvents. In addition, we have also shown that by selecting the right counter ion, ionic liquids offer reduction of the dose-dependent toxicity of actives that otherwise cause skin irritation. I will present examples of these applications of ionic liquids, which collectively demonstrate that ionic liquids hold promise as a novel and unique platform for skin applications.

Research Spotlight—Computational Modeling for Intradermal Delivery

10:55 **Update on Computational Model for Dermal Transport and Clearance**

Dr. Gerald B. Kasting, Professor of Pharmaceutics and Cosmetic Science, University of Cincinnati

Unlike transdermal delivery, intradermal delivery is largely controlled by the physiology and transport properties of the lower skin layers. Clearance of an injected drug is governed by the interplay of hydrostatic and osmotic pressure, blood capillary density and permeability and lymphatic flow, as well as compound specific factors such as partitioning and protein binding. These factors vary between individuals and from site-to-site. We have developed a spreadsheet-based computational model for dermal clearance and transport that incorporates both the physicological and chemical-specific factors; thus can be used to guide the development of intradermal and (with appropriate modifications) subcutaneous injection technology. Example calculations involving specific macromolecules will be presented.

11:35 **Heat Effects and IVIVC in Transdermal and Topical Drug Delivery**

Audra Stinchcomb, Ph.D., Chief Scientific Officer and Founder of F6 Pharma Inc.; Professor, University of Maryland

An in vitro model that exhibits IVIVC is a powerful tool in biopharmaceutical drug development because it can efficiently predict drug product performance in vivo. While the concept of IVIVC has been utilized most often for oral dosage forms, demonstrations of IVIVC with in vitro models used for other dosage forms are emerging. The present investigation used multiple approaches to develop a Level A IVIVC for Transdermal Delivery Systems (TDS). Additionally, the effect of transient heat exposure on the rate and extent of TDS drug delivery was concurrently evaluated. Two model drug molecules, nicotine and fentanyl, with different physicochemical characteristics (e.g. log P) were evaluated in the current study. Early study results will also be reported for lidocaine and buprenorphine IVIVC.

12:15 ***Complimentary Lunch Sponsored by:***

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1:15 **Advancements in Coating of Adhesives for Transdermal Drug Delivery**

Scott Zwierlein, Coating Engineer, Frontier LLC

The quality and function demanded of Transdermal Drug Delivery Systems is becoming ever more stringent, both from government requirements and end users. Because of these increasing demands the application or coating of the transdermal adhesive has had to improve. The application of the adhesive to the liner must be done cleanly and accurately. With the high cost of active ingredients, it is also imperative that waste be minimized so that the manufacturer can stay competitive in the marketplace. Our presentation will discuss the advancements in the coating of the Transdermal Drug Delivery Adhesives by comparing older, traditional methods such as roll and comma coating with new, alternative methods like slot-die coating. We will also discuss techniques for minimizing yield losses and scrap throughout the coating and converting process. Some topics include Skip Coating, precision die cutting, on-line thickness measurement and inspection.

1:45 **Advances in Intradermal Drug Delivery**

Glen Zimmermann, Director of Product Management, West Pharmaceutical Services

Currently, IM and SC are the most common methods for delivery of non-infused drugs however, the skin contains a high concentration of antigen presenting cells, making it an ideal location for injection. These cells perform an essential role in processing incoming antigens, resulting in powerful immune system responses. Delivery of vaccines to the epidermis or dermis may result in superior immune responses when compared to IM or SC injections. In addition to the enhanced immune response in patients, ID delivery offers a variety of benefits to pharmaceutical manufacturers, including dose sparing, increased availability of limited or expensive antigens, and reduced cost per dose.

Typically ID injection is administered using the Mantoux technique, which requires special training and may not effectively target the skin resulting in delivery to the SC tissue (too deep) or leakage (too shallow). The difficulty associated with training and the inconsistency of injection efficacy have deterred medical practitioners from using ID injection as a common immunization method. In response to this, new devices have immerged to eliminate the challenges associated with performing an ID injection. This presentation will review some of the more recent advances in ID drug delivery systems.

Regulatory & Safety Issues—Extractables/Leachables Testing of TDD and IDD Systems to Meet FDA Requirements

2:15 **Extractable and Leachable Testing for Transdermal Drug Delivery Systems: How to Resolve FDA Deficiency Situations Related to Those Issues**

Gyorgy Vas, Ph.D., Trace Organic Analytical Group, Intertek Pharmaceutical Services (Contributing Authors: Louis Fleck, Howard Carpenter.)

Transdermal drug delivery systems are relatively complex pharmaceutical products. The formulation contains multiple excipients and in addition a dermal contact adhesive. The performance of the delivery systems depends on the quality of the dermal adhesive and the formulation, which delivers the drug on a pre-determined rate. The dermal delivery route is getting more and more popular, since the effect of the delivered drug can be localized, which may reduce the systemic side effects. However since the formulation has extended contact time, besides the dug is being delivered excipients, degradation products and packaging related components can also be "delivered" with the same route of administration. The extractable testing of transdermal systems are straightforward, does not requires "out of box" thinking. The leachables testing requires more complex approaches, as the regulatory expectation is to test the finished products with biologically relevant extraction media.

The presentation will focus on different test approaches, to present options for leachable testing, how to evaluate the actual leachables and validate analytical methods what are requires non-routine extraction methods and as well detection capability down to ppb level. The complex formulation combined with the low level testing requirement are very challenging analytical task. Component identification, analytical method development and validation are not as simple as for the components present at a ppm level or above. The presentation will also presenting case studies and solutions for non-conformance situations related to TDS systems.

2:55 *Afternoon Networking Break*

3:10 **A Framework for the Biocompatibility Safety Assessment of a Transdermal Drug Delivery Device**

Andrew T. Blakinger, Manager, Eurofins Lancaster Laboratories / Eurofins Medical Device Testing (Contributing Authors: Charles E. Ducker, Michelle Kolodziejski, Daniel Merrill, Mai N. Jacques, Matthew Woods, Christopher Scott, and Thomas C. Lehman.)

The purpose of this talk is to present a framework for the safety evaluation of transdermal patches as a drug delivery device highlighting the importance of the extractables and leachables assessment. The safety evaluation of this type of medical device will be predicated based on biological assays and assessment of potential extractables and leachables. The biological assays consist of cytotoxicity testing, irritation testing and sensitization testing. The extent of this testing can be dependent on the initial cytotoxicity/ extractables and leachables evaluation. Assessment of extractables and leachables for medical devices is described in ISO 10993-12, which details recommendations for the temperature, surface area to volume ratios, and solvents to be used for the extraction. As a case study, three unique transdermal patches, each with different compositions, were extracted utilizing a customized technology. Compositional evaluation of the extraction results combined with cytotoxicity test results will be presented and discussed in light of developing a comprehensive biocompatibility evaluation strategy.

Critical Issues—IVPT & IVRT of Transdermal and Topical Products

3:50 **Evolution of the in vitro Permeation (IVPT) and in vitro Release (IVRT) Tests—Coming of Age**

Paul Lehman, VP and Head of Dermal & Transdermal Research Services, QPS Holdings, LLC

Since the innovation of the Franz Diffusion Cell and the Finite Dose Model by Dr. Thomas Franz, c1974, their simple and elegant value has matured over the years to become a more complex contribution to the advancement of semi-solid and transdermal delivery systems to the industry. Today, the use of the diffusion cell is at the threshold of being fully recognized as a surrogate model for the determination of bioequivalence for topical semi-solid formulations. However, the complete passage into full acceptance and recognition requires the same scrutiny that any other surrogate model requires, namely validation, whether for IVPT or IVRT. Validation requires the demonstration of procedural standardization, sensitivity, selectivity, reproducibility and robustness. These factors will be discussed, and as to whether they actually do contribute to substantiating the validity of the models.

4:30 *Close of Program*

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