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PharmaED's

Transdermal Drug Delivery Systems

Examine Recent Developments in Transdermal Drug Delivery

MARCH 15-16, 2012, RACQUET CLUB OF PHILADELPHIA, PHILADELPHIA, PA

Key Learning Objectives:

- Practical Considerations for Expanding the Range of Drugs and Vaccines for Delivery Using Transdermal Systems
- Explore Transdermal Drug Delivery Systems as a Viable Alternative to Oral, Intra-Muscular or Intra-venous Injection
- Understand How FDA Regulates Transdermal Drug Delivery Technologies for Investigational and Marketed Products
- Explore Novel Applications of Transdermal Drug Delivery Technologies
- Overcome Obstacles and Achieve Efficacy in Active Transdermal Delivery Platforms
- Cost Considerations in the Development and Production of Transdermal Delivery Systems
- Understand Therapeutic Advantages for Transdermal Delivery of Biopharmaceutical and Vaccines
- Learn How New Technologies are Expanding the Scope of Transdermal Delivery to Include Hydrophilic Macromolecules

Featuring Representation From:

Eakins and Associates, Inc.
BD Technologies
University of Mississippi
Xel Pharmaceuticals, Inc.
AllTranz Inc.
PATH
Biologics Consulting Group
3M Drug Delivery Systems
Advanced Medical Technologies
University of Kentucky College of Pharmacy
Polytherapeutics, Inc.
Research Institute for Health Sciences, Chiang Mai

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Thursday, March 15, 2012

9:00 *Chairperson's Welcome and Opening Remarks*

9:15 **Challenges and Considerations in Development of Generic Transdermal Products**

Dr. DanyiQuan, Chief Scientific Officer and cofounder, Xel Pharmaceuticals

Unlike the product development of new transdermal products, the risk of total failure for generic transdermal product development is low because the safety, efficacy and skin penetration profiles have been already established; however the cost and time efficiency are more important and critical because of much lower profit margins and competition with other generic manufacturers. The possible obstacles to the efficient product development of a generic transdermal product can occur at every stage during the development process, especially in the formulation development stage.

Generic transdermal products have more challenges to develop because of their complexity of reference products compared to the generic solid dosage form products. Complex reference products may include active ingredients, pressure sensitive adhesives, chemical penetration enhancers, co-solvents, other polymers and excipients, and rate-controlling membranes, which can directly affect the technical parameters and performance of the generic transdermal products, such as patch size, adhesion, wearing properties, skin permeability, dissolution (release rate) profiles, physical and chemical stabilities, and skin irritation. Therefore, quality by design become an essential part of the modern approach to achieve an efficient and successful generic transdermal product development

This presentation will cover:

- Challenges and considerations of development of generic transdermal products
- Industry perspective of generic transdermal product development
- Key design points in the formulation development stage
- How to catch the potential problems in the early development stage?

10:15 *Refreshment break*

10:30 **Intradermal Delivery and the Developing World**

Darin Zehrung, Technical Officer, Portfolio Leader, Vaccine Delivery Technologies, PATH

PATH is an international nonprofit organization that creates sustainable, culturally relevant solutions, enabling communities worldwide to break longstanding cycles of poor health. By collaborating with diverse public- and private- sector partners, PATH helps provide appropriate health technologies and vital strategies that change the way people think and act to improve global health and well-being.

For more than 20 years, PATH has worked with immunization technologies for use in low-resource settings. PATH's Vaccine Delivery Technologies Group takes a multi-disciplinary approach to product development, ensuring that new technologies for vaccine administration are acceptable to users, cost effective, and based on sound and tested science. PATH is currently working to identify current and future applications for intradermal immunization in developing countries, with a particular focus on alternative delivery devices. Intradermal delivery represents potential benefit to international public health, but must be weighed against operational challenges such as reformulation, vaccine presentation, development of intradermal delivery devices, injection safety and health care worker training requirements.

11:30 *Luncheon and Exhibit Viewing*

1:00 **PharmaDur® Virtual Patch Technology – Expanding the Scope of Transdermal Drug Delivery**

Kishore R. Shah, Ph.D., President, Polytherapeutics, Inc.

PharmaDur® is a graft copolymer having a hydrophilic main chain with some carboxyl functionality and hydrophobic polymeric graft chains. The copolymer exhibits a combination of bioadhesive and controlled release properties on account of its unique structural characteristics. When a dermatological vehicle, e.g. cream, lotion, or a gel, formulated with PharmaDur® polymer is applied to skin, it forms an imperceptible and invisible hydrogel film ("A Virtual Patch"). PharmaDur® film on skin serves as matrix for the drug and other non-volatile excipients for the product formulation. The polymer film and the drug contained therein are retained on skin for 24+ hours. Unless the film is physically washed off, it is not removed by perspiration or articles of clothing. The polymer film provides continuous release of the drug by a process of diffusion for transdermal delivery to the body. Thus, it functions as a virtual "patch" without the limitations of plastic patches. The "virtual patch" provides following key advantages:

- Drugs having high dosage or those with low skin permeability can be effectively delivered by the PharmaDur® "virtual patch" since it can be applied over a large area of skin (~ 300 to 500 cm2).
- Its long lasting retention on skin enables it to provide all day sustained therapeutic efficacy with once/day application, which also improves consumer convenience and compliance.

- Reduction of undesirable side effects due to avoidance of "peaks and valleys" in systemic drug concentrations typically found with oral drug administration.
- Many drugs, which are not suitable for transdermal administration using conventional plastic patches and semi-solid dosage forms, can be delivered transdermally using the PharmaDur® virtual patch.

2:00 **Topical Drug Delivery to The Nail Apparatus**

Narasimha Murthy, Associate Professor, University of Mississippi School of Pharmacy

Nail diseases such as onychomycosis and nail psoriasis are prevalent health issue in the western world. The nail diseases vary from mild to high severity and could worsen the quality of life of patients particularly in immune compromised patients. Although, oral administration of huge doses of antifungal and antipsoriatic drugs is effective, it is associated with severe gastric and systemic side effects. Topical therapy has been poorly successful due to lack of efficient technologies that can deliver and maintain therapeutically effective amount of drugs In the nail apparatus. In the recent decade, a lot of research has been going on to develop innovative passive and active drug delivery approaches to deliver drugs into the nail apparatus. This presentation covers the nail diseases, properties of nail plate and nail fold, topical delivery approaches and early stage technologies of ungual and trans-ungual drug delivery.

3:00 ***Afternoon Break***

3:15 **Assessing New Physical Technologies for Transdermal and Intradermal Delivery of Therapeutic Agents**

Dr. Ajay Banga, Professor and Department Chair in the College of Pharmacy and Health Sciences in Atlanta

In recent years, there has been increasing interest in enhancement technologies that can expand the scope of transdermal delivery to hydrophilic molecules and macromolecules. These molecules do not normally pass through the skin unless enabling technologies are used. Some of the enabling technologies include iontophoresis, phonophoresis, or microporation. Recent innovations in these technologies, especially for iontophoresis and microporation, will be presented. Microporation involves the creation of micron-sized micropores or microchannels in the skin which can then allow the transport of water soluble molecules. Skin microporation can be achieved by microneedles or by using thermal, laser, or radio-frequency ablation. We have used soluble microneedles made of maltose as well as metal microneedles to demonstrate delivery of small molecules, large proteins, or even micron sized particulates. Iontophoresis involves the application of small amounts of physiologically acceptable currents to drive ionic drugs into the skin. We have demonstrated iontophoretic delivery of several conventional drug molecules and polypeptides. We have also used a combination of iontophoresis and microneedles to show that charged drug molecules can be propelled via microchannels created in the skin by microneedles to achieve delivery flux higher than that could be achieved by either technique alone.

- Learn how new physical technologies are expanding the scope of transdermal delivery to include hydrophilic molecules and macromolecules
- Learn the success and failures of iontophoretic delivery systems developed and marketed over the years
- Learn about the recent excitement and activity centered around bringing a microneedle patch to the market

4:15 **Progress and Promise Towards Delivering Antigens for Cutaneous Vaccination**

Bruce G. Weniger, MD, MPH, CAPT, USPHS (ret.), International Professor, Research Institute for Health Sciences, Chiang Mai University, Associate Editor, Vaccine

Proven and promising advantages of cutaneous vaccination over conventional and other alternative routes include minimal invasiveness and thus lessened risk from unanticipated serious local reactions, certain delivery that does not require patient cooperation, avoidance of needle risks and phobia, wide separation of simultaneous antigens, and the potentials for pain-free patient preference, dose-sparing for scarce or expensive antigen, rapid mass campaigns, decreased storage volume per dose, and thermostability for overburdened cold chains.

The skin was variolated as early as the 16th Century, and remains the primary target for smallpox and BCG vaccines. The literature documents the classical intradermal (ID) Mantoux method for over a dozen vaccine types. Excellent results for rabies justify use in developing countries to economize on post-exposure prophylaxis. Generally good results for influenza since 1937 suggest a dose-sparing strategy during vaccine shortage. Salk's original (IPV) polio vaccine was ID, a route once used routinely in Denmark. Recent studies suggest this strategy for the planned conversion from cheap OPV oral

vaccine to expensive IPV after initial eradication. Early studies found mixed to poor results for hepatitis A, hepatitis B, cholera, and measles vaccines. In the last decade, clinical trials studied antigens to protect against dengue, seasonal and avian influenza, hepatitis A and B, HIV, malaria, meningococcosis, polio, travelers' (enterotoxigenicE. coli) diarrhea, and tuberculosis, as well as immunotherapies for various cancers.

Novel delivery systems poke, strip, abrade, vaporize, bombard, vibrate, shock, or otherwise permeabilize the stratum corneum, the principal anatomic barrier to access antigen-processing epidermal Langerhans cells or dermal dendritic cells, which then migrate to deeper lymphoid tissue to continue the immune response.

U.S.-licensed devices for cutaneous delivery include jet injectors and a recent mini-needle syringe for influenza. Investigational methods involve coated microtines, hollow and dissolving microneedles, passive-diffusion, supersonic gas, and thermo- and electro-poration.

This presentation will discuss:

- Classical Intradermal (ID)
- Delivering the First Vaccine – Smallpox
- Jet injection for Cutaneous Delivery
- Mechanical Disruption of Stratum Corneum
- Coated Solid Microneedles
- Hollow Mini – and Microneedles
- Dissolving Microneedles
- Issues; Relative Pros and Cons
- Other (Kinetic, Electromagnetic, Chemical, etc.)

5:00 *Close of Day One*

Friday, March 16, 2012

9:00 **FDA Regulation of Transdermal Drug Delivery Systems**

Michael Gross, Ph.D, RAC, Senior Consultant, Biologics Consulting Group

This presentation will consider how the FDA regulates investigational and marketed transdermal drug delivery technologies that follow two different development and regulatory pathways, (1) drug products and (2) combination products which combine drugs or biologics and medical devices. Principles and recommendations on development, registration, and compliance for passive (i.e., osmotic reservoir and matrix) and active (e.g., iontophoresis, microneedle) transdermal drug delivery systems will be discussed including, product jurisdiction, investigational exemptions, marketing applications, clinical investigations, labeling, quality systems, safety reporting and the reporting of post-approval changes. The presentation will also cover key points from the recent DIA-FDA meeting on Improved Development and Regulation of Transdermal Systems.

10:00 **Pore Lifetime And Formulation Aspects In Microneedle-Assisted Delivery**

M. Milewski, N.K. Brogden, S.L. Banks, and A.L. Stinchcomb, Professor University of Maryland & Chief Scientific Officer AllTranz Inc.

Transdermal microneedle systems have become a very popular means of delivering skin impermeable drugs through the stratum corneum at therapeutic rates. Most of the previous research on microneedle systems has focused on optimization of the microneedle geometry. Our approach to microneedle-assisted delivery research has been in the following four areas, which will be presented:

1. Investigation of prodrugs and salt forms with optimal physicochemical properties for drug flux after microneedle treatment
2. Investigation of viscosity and other formulation factors that influence drug flux after microneedle treatment
3. Investigation of micropore lifetime using transepidermal water loss (TEWL), impedance spectroscopy, and pharmacokinetic analysis
4. Investigation of micropore lifetime after treatment with COX inhibitors

11:00 *Mid-morning Break*

11:15 **Past, Present and Future of Transdermal Drug Delivery Systems**

Michael Eakins, President, Eakins & Associates, Inc.

This presentation will cover the rise of transdermal drug delivery systems as a viable alternative to oral, intra-muscular or intra-venous injection. It will provide an overview of the second- and third-generation systems and strategies and evaluate whether the recent rise in the number of drugs administerd in transdermal delivery systems will continue at the same pace or slow down due to competition from other drug delivery systems.

12:15 *Luncheon and exhibit viewing*

1:30 **Quality & Safety of Transdermal Delivery Systems**

Dr. DanyiQuan, Chief Scientific Officer and cofounder of Xel Pharmaceuticals

The global 2010 transdermal market for patches alone reached $9.5 billion, and transdermal is poised for continuous growth as innovative technologies are being developed. However, over the past years, various product

quality problems have been reported by FDA, practitioners and patients. Some of these quality problems have safety and efficacy implications that have led to the recall of numerous batches of products, and in some circumstances, the temporary or permanent removal of the product from the market. Transdermal drug delivery systems have complex aspects for their quality, safety and efficacy. Therefore, to reduce some of these risks, R&D scientists should apply an enhanced product design and development approach – especially Quality-by-Design (QbD) to each stage (e.g. formulation development, clinical trial and manufacturing process) during the transdermal product development for both new products and generic products.

This presentation will cover:

- Linking quality to safety for transdermal drug delivery systems
- Understanding on FDA perspective on quality and safety considerations
- Quality cannot be tested into transdermal products; it has to be built in by design
- Practical QbD (Quality-by-Design)

2:30 **Immune Response and Safety for Intradermal Influenza Vaccination by Needle-free Jet Injection in Infants and Toddlers**

Bruce G. Weniger, MD, MPH, CAPT, USPHS (ret.), International Professor, Research Institute for Health Sciences, Chiang Mai University, Associate Editor, Vaccine

This presentation will discuss:

- Intradermal (ID) route: dose-sparing for influenza and some other vaccines
- Dose-sparing may protect larger numbers with
- Scarce or expensive vaccines
- Traditional MantouxID injection by needle-syringe (N-S) is difficult and tedious
- Multi-use-nozzle jet injectors (MUNJIs) in 1950s-1970s – administered tens of millions of ID doses of smallpox, yellow fever, and BCG vaccines
- A new generation of safe, disposable-syringe jet injectors(DSJIs) since mid-1990s
  – Avoid bloodborne-pathogen cross-contamination risk of MUNJIs
  – Reduce dangers and drawbacks of N-S

3:30 **Use of ID Delivery for Targeting of the Lymph Systems for Imaging, Immunotherapy, and Oncology Applications**

Ronald J. Pettis,Ph.D., Principal Scientist, Sr. Manager Infusion Technology Diabetes Care/Advanced Medical Technologies

4:30 ***End of Conference***

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Venue Phone:	(215) 772-1541
Hotel Room Block:	Radisson Plaza Warwick
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