COST-EFFECTIVE APPROACHES FOR SUCCESSFUL GENERIC DERMAL DRUG PRODUCT AUTHORISATIONS

In this article, Prof Marc Brown, PhD, Chief Scientific Officer, Jon Lenn, PhD, Senior Vice-President US Operations, and Jeremy Drummond, PhD, Senior Vice-President Business Development, all of MedPharm, discuss various methods and advantages of *in vitro* bioequivalence studies for topical skin application, and how MedPharm's unique technologies and experience can be invaluable in the effective development of generics in this field.

Dermal products for topical application are an attractive option for pharmaceutical companies seeking to address unmet needs and generics developers hoping to broaden their market coverage. The topical dermal market for pharmaceutical products is currently estimated to be over US$18 billion (£13 billion),[1] a small but significant niche in the overall pharmaceutical market.

The pharmaceutical industry is highly regulated and significant investment is required to demonstrate the quality, efficacy and safety of any new product before the authorities will grant market authorisation. Once valid patents have expired it is imperative that new generic entrants can demonstrate exactly the same, or in some cases improved, standards to ensure that there is no compromise for patients. Traditionally this is done by showing that the generic product delivers the same efficacy and safety profile in clinical trials.

In the case of topical products for the treatment of skin disease it has been typically necessary to demonstrate therapeutic bioequivalence. For other routes of delivery, including transdermal patches, where the delivery is systemic, only a demonstration of pharmacokinetic bioequivalence is required by the authorities.

Clinical trials remain time consuming, expensive and risky, and can be a significant barrier to generic introduction for products within all but the largest markets. The variability in skin adds inherent risks to any clinical trial on top of the expense. As the skin also responds to most excipients there is no true placebo, just vehicle components that are accepted to have some effect. This makes primary endpoints more difficult to meet, further increasing the risk of failure. In turn this creates a challenge for governments wanting to promote the introduction of topically applied generics as a way of reducing their healthcare bills, whilst at the same time being clearly obligated to register generic products without any additional risk to patients.

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A recent analysis by the US Government Accountability Office of drug pricing between 2010 and 2015 showed that topical generic drug prices had increased by an average of 276%, whereas all other routes of delivery (oral, intravenous and ophthalmic) had seen no significant change.[2] This was directly related to lack of generic competition and the height of barriers to entry for new topical generic products.

THE CHANGING GUIDANCE FROM REGULATORY AUTHORITIES

MedPharm's experience is that regulatory authorities on both sides of the Atlantic are becoming more open to non-clinical or *in vitro* approaches. These approaches allow the bioequivalence of a generic topical drug product with the established reference listed drug (RLD) to be demonstrated with a high degree of confidence without the need for any clinical data.

At recent workshops, the US FDA has openly expressed a desire to have dialogue with those companies submitting topical generic applications. They have now introduced pre-ANDA meetings akin to pre-IND meetings to allow generics companies to hear opinions on their approach to bioequivalence before they complete and submit the full generic application.

In October 2017, the FDA introduced new draft guidance for four topical semi-solid products in addition to acyclovir cream, in order to stimulate generic entrants.[3] The guidance stipulates the testing data the agency expects to see in order for it to approve products without supporting therapeutic bioequivalence data. Additionally, the agency has produced guidance notes for five solution-based foam aerosols.[4] More can be expected to follow as the FDA establishes the standards needed to show equivalence using *in vitro*/*ex vivo* performance testing models.

The FDA is following its traditional approach of providing published guidance on a product by product basis. Recent communications with the UK MHRA suggest that European authorities will be focusing on a universal guidance for topical generic product submissions. All indications suggest that the MHRA and EMA will be open to submissions for topical generics using *in vitro* models to demonstrate bioequivalence, provided that they are based on sufficient scientific rigour and validation. The procedure of using scientific advice meetings is well established at the EMA, as well as at specific European countries agencies (e.g. MHRA, BPharm) to provide opinions on generic submission strategies.

In MedPharm's experience, it is important to discuss any development strategy for a generic topical product in which *in vitro* bioequivalence is being used early on with the appropriate regulatory authorities. As an example, MedPharm would typically create a proof-of-concept dataset to present to the relevant agency to support the approach being taken. MedPharm supports clients at agency meetings and in all cases regulatory authorities have demonstrated an openness to the approach, as long as the proposed studies can be demonstrated to be conducted with sufficient scientific rigour and there are no safety concerns.

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A COST EFFECTIVE APPROACH TO DEMONSTRATING BIOEQUIVALENCE

To date, MedPharm has helped several clients convince regulatory authorities that the scientific data obtained from *in vitro* studies, demonstrating equivalence at all levels between the originator topical product and the generic product, is sufficient to demonstrate bioequivalence between the two and therefore make the need for costly clinical trials unnecessary.

MedPharm's approach to establishing a submission package acceptable to regulatory authorities revolves around two key areas:

1) Reverse-engineering of the originator product to establish concentrations and grades of the excipients listed in the patient information leaflet (PIL).
2) Rigorous performance testing to demonstrate that the generic product behaves in the same way as the originator product or RLD.

The excipients in the originator product are listed in the PIL. Concentration ranges can be established by appropriate and validated analytical methods and should be within ±5%. It is often difficult to analyse the grade of any excipient and this can have a significant bearing on product performance. As a result, MedPharm relies on its extensive formulation experience to select the most appropriate excipient grade and source. Furthermore, MedPharm will help establish the most appropriate manufacturing process based on its experience and subsequently this can be refined and validated using rigorous process development methodology (e.g. Quality by Design, Design of Experiments).

Core to the activity of developing a formulation that is fundamentally as close to the originator product/RLD as possible is ensuring that the products are qualitatively, quantitatively and structurally the same. FDA guidance[2] classifies this as:

- Q1: Qualitative Similarity
  - same components.
- Q2: Quantitative Similarity
  - same amounts of the same components.
- Q3: Structural Similarity
  - same amounts of the same components arranged in the same way.

The class of excipients (Q1) used in the RLD is stated in the PIL and is therefore in the public domain. Reverse engineering is used to establish the relative amounts of the excipients (Q2) to ±5% and where possible the grade and origin of the excipient. Q3 relates to the micro-structure of the formulation. This requires demonstration that the drug product has, for example, the API in the same polymorphic form if it is in suspension, a cream's emulsion has the same particle size range or the semi-solid drug product has the same rheological characteristics.

It is the performance testing that then demonstrates the equivalence of product performance. First, *in vitro* release testing (IVRT) is developed and validated to show the drug in the generic product has the same release characteristics as the RLD. Regulatory authorities are now requiring this as a quality control tool and mandate its incorporation into the release and stability

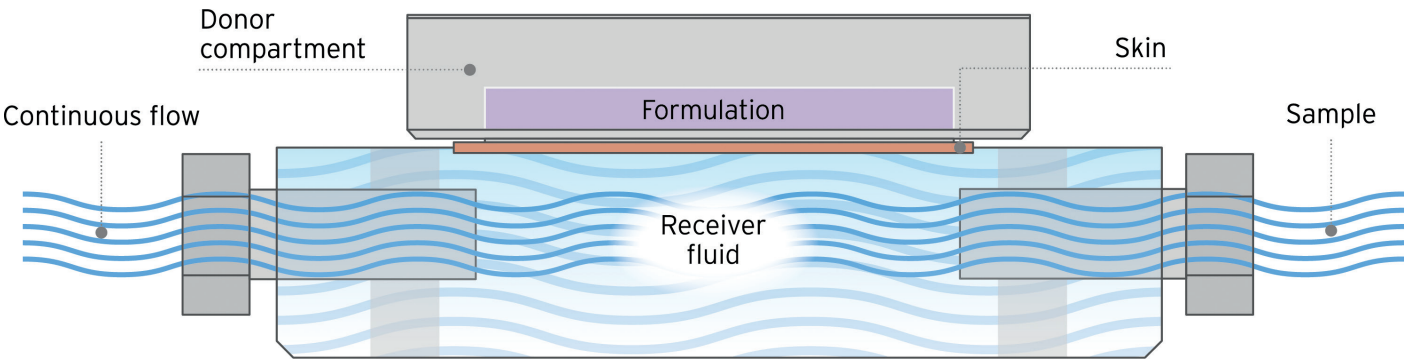

Figure 1: Schematic representation of a MedFlux-HT® cell.

specifications. Importantly the IVRT must be validated to demonstrate that the method is sufficiently sensitive for discrimination and robust enough to justify that the API release from the two formulations is the same. Recently MedPharm has developed a 24-cell, automated IVRT system, MedStat-HT™, to improve the efficiency and robustness of the method and is engaged in discussions about its use in future submissions.

IVRT is used to investigate a drug's release from the topical formulation. It does not provide any indication of how the formulation impacts the drug's absorption across the skin. This is another key component to a product's performance or equivalence so, to determine it, the appropriate methodology, *in vitro* penetration/permeation testing (IVPT), including a diffusion cell, must be utilised. MedPharm has two options here:

1. Traditional vertical diffusion cells or static Franz cells.
2. MedPharm's unique flow-through cells, MedFlux-HT® (Figures 1 & 2).

"The benefits of this approach are clear: clients can enter generic markets with a significantly lower investment cost and in a shorter timeframe. It is also clear that regulatory authorities are increasingly open to accepting bioequivalence using *in vitro* performance models for dermal products."

With MedFlux-HT, the skin is carefully and continually perfused and sample collection is automated using a high-throughput design to minimise artefacts, ensure sink conditions, reduce sampling errors and allow for continuous and rigorous sample collection. Both models allow for the permeation of the drug from the generic and originator product to be compared. The key advantage of the MedFlux-HT model is that, by having continuous clearance, it is a closer model to the clinical setting and, through automation, offers the ability to demonstrate equivalence within potentially tighter confidence limits. In both cases the layers of the skin can subsequently be analysed for drug content to show equivalence in drug penetration (skin layers) as well as permeation (receiver fluid).

These models typically require highly sensitive bio-analysis in order to detect the ultra-low drug levels inherent to all topical applications. MedPharm has experienced drug metabolism and pharmacokinetics (DMPK) bio-analysts with a specialised knowledge in the challenges of detecting low levels of drug in skin and other matrices using liquid chromatography mass spectrometry (LC-MS)/mass spectrometry (MS).

As with IVRT, it is important to validate the IVPT method chosen in order to demonstrate accurately that the generic and originator products are penetrating at the same rate and permeating in equivalent levels to the different layers of the skin.

Fundamentally, neither IVRT nor IVPT can demonstrate whether the drug is biologically active, even if it is detected in the skin layers. To address these limitations, MedPharm has developed a series of *in vitro* disease or pharmacodynamic (PD) activity models to demonstrate the equivalence of products for the treatment of skin infections (e.g. athlete's foot, onychomycosis, acne and herpes), inflammatory skin diseases (e.g. psoriasis, atopic dermatitis) or bacterial infections. Custom models can also be developed because these *ex vivo* human skin models can be kept in a functional state for up to ten days using proprietary methods. In addition, these models have the added of advantage of allowing the drug to be quantified in the skin over time via

Figure 2: MedPharm's unique flow-through cells in MedFlux-HT® are automated to allow for reduced sampling errors and continuous and rigorous sample collection.

pharmacokinetics (PK). This means that, in the same tissue, the PK and PD activity can be assessed simultaneously to create a PK/PD analysis in a mimetic disease model.

Yet again it is crucial to demonstrate to regulatory authorities that these disease activity models have an appropriate level of validation. By combining all of these approaches and tools a generic product's sameness with an RLD can be assessed and compared with an originator qualitatively, quantitatively, structurally and in terms of drug release, absorption and biological activity.

THE BENEFITS OF THE *IN VITRO* BIOEQUIVALENCE APPROACH

The benefits of this approach are clear: clients can enter generic markets with a significantly lower investment cost and in a shorter timeframe. It is also clear that regulatory authorities are increasingly open to accepting bioequivalence using *in vitro* performance models for dermal products. Such an approach lowers the barriers to market entry and hence allows governments to lower healthcare bills more swiftly than they otherwise could. Furthermore, it allows generic producers to enter markets that they would otherwise be precluded from because of the prohibitive expense of conducting suitable clinical therapeutic bioequivalence trials.

These approaches are strictly aimed at demonstrating the exact equivalence of the generic product with the originator/RLD. In this approach, equivalence must be demonstrated even when the originator's performance is known to be sub-optimal. There are opportunities through formulation for generic companies to register products which have improved performance over the originator, which may allow for faster and greater market penetration and some price premium. Currently this must be demonstrated though a therapeutic clinical trial. In such a scenario, the use of the performance models described here is also key in de-risking the decision to invest in this clinical trial. Unless a meaningful difference can be demonstrated using IVPT and/or disease activity models, it is very unlikely that endpoints showing clinical improvement will be met in any subsequent clinical trial.

ABOUT THE COMPANY

MedPharm is a leading contract provider of topical and transdermal product design and formulation development services. MedPharm has expertise in reducing risk and accelerating development times for generic and proprietary pharmaceutical customers through their unique, cost effective and industry-leading performance testing models. Well established as a global leader in dermatology, nail, mucosal membrane and transdermal product development, MedPharm can also offer innovative solutions for ophthalmic and airway preparations recognised for their scientific rigour by regulators and investors. MedPharm has fully established R&D centres in the US and UK and has its global headquarters in Guildford, UK.

ABOUT THE AUTHORS

Marc Brown co-founded MedPharm in August 1999 and has been the guiding force behind all the company's scientific developments and intellectual property. He has been Professor of Pharmaceutics at the School of Pharmacy, University of Hertfordshire (UK), since 2006 and has honorary professorships at the University of Reading (UK) and King's College London. Prof Brown has over 200 publications and 26 patents describing his work. His research interests lie mainly in drug delivery to the skin, nail and airways. To date, he has been involved in the pharmaceutical development of more than 38 products that are now on the market in Europe, America and Japan.

Jon Lenn has direct responsibility for MedPharm's operations in the US based in Durham, NC. Since joining in 2015, he has led MedPharm's development of cutting-edge performance models for assessing penetration and activity of clients' products targeted towards key biochemical pathways. He has over 15 years' experience in developing dermatological projects and has been directly involved with the development and approval of eight products. Dr Lenn received his PhD on the topical delivery of macromolecules from the University of Reading (UK).

Jeremy Drummond joined MedPharm in February 2017. He has spent over 20 years leading the commercial supply of product and services to pharmaceutical companies across the globe. He is responsible for leading revenue growth, key client relationships and marketing MedPharm to its global customer base. He started his career as a technical formulator and has a PhD in organic chemistry from the University of Cambridge (UK).

REFERENCES

1. *Evers P, "Skin Disease Treatment Technologies and Global Markets". BCC Research, Jan 2016.*
2. *Raney SR, "Strategies to Improve Patient Access to High Quality Topical Products". AAPS Workshop – Dermatological Drug Products: Developmental & Regulatory Considerations, November 2017. Accessed Jan 3, 2018. https://zerista.s3.amazonaws.com/item_files/38d0/attachments/413001/original/311_2729.pdf*
3. *"Draft Guidance on Dapsone". US FDA, Oct 2017 www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM428205.pdf*
4. *"Draft Guidance on Clobetasol Propionate". US FDA, Feb 2011. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM244373.pdf*

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