PEER REVIEWED

Regulatory and Developmental Complexities Around Demonstrating Bioequivalence for a Topical Generic Product

Increasing Patient Access to High-Quality Topical Products

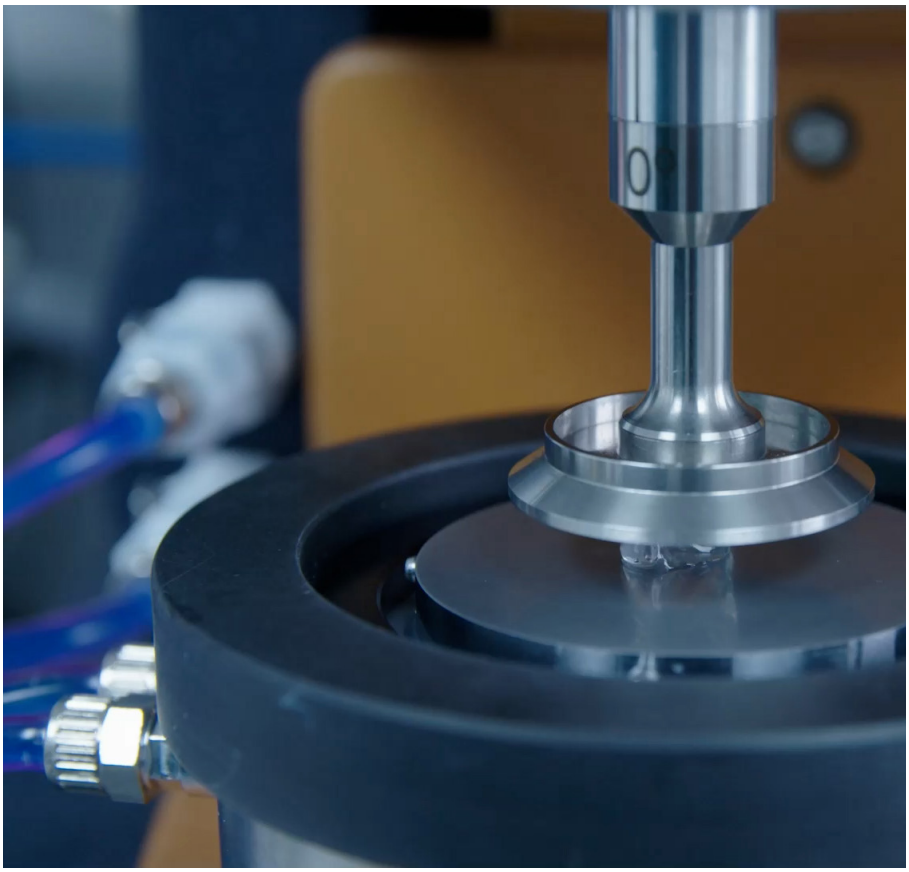
The topical dermatology market, although niche, was estimated to be valued at approximately $20.4 billion in 2020.[1] In a study from 2010–2015, over half of the topical drug products experienced a price increase and the average price of topical generic drugs was 276% higher by the end of that period. This is being driven by the lack of competition among generic manufacturers, where approximately 80% of topical dermatological drug products have very few competitors or no approved generics at all. Lack of generic products can be attributed to the complexity of developing topical dermatological drug products, low market volumes, and/or the risk and expense of clinical endpoint bio-equivalence (BE) studies.

Topical dermal formulation development is inherently challenging due to the distinct characteristics of dermal drug delivery, including the complex characteristics of the skin barrier (e.g., location, age, condition). Additionally, formulations are often applied to diseased skin that is likely perturbed or influenced by external factors (e.g., temperature, humidity, occlusion). Another distinct characteristic of topical formulation development is the complexity of the product. For example, the number of excipients required for a topically applied product can make development difficult. Each excipient used in a product can impact the formulation's irritation and sensitisation, bioavailability, penetration, dose homogeneity, drug solubility and stability, and drug product physical and chemical stability (quality). In some cases, these properties can be markedly different between excipient suppliers, grade, and age making the development of exact generic copies of such formulations extremely difficult without commensurate excipient knowledge.

In efforts to make high-quality, affordable medicines available to the public, regulatory agencies have released guidances to create a modular framework for *in vitro* bioequivalence (BE) testing of topical products in lieu of clinical trials. The FDA released a draft guidance in 2016 on acyclovir cream which has served as a reference point for the other product-specific guidances (PSGs) that continue to be published by the FDA within 18 months of an NDA. The European Medicines Agency (EMA) released a similar general draft guideline on quality and equivalence of topical products in 2018. These two guidances serve as the foundation for what has been a flurry of activity in the generic space for topical drug products. As generic companies would not have to undergo the same rigorous clinical studies that are required of the brand-name product, generic products can be developed, approved, and pushed to market more quickly. This can lower the cost of development by up to 85% when compared with the cost of developing the innovator product. Additionally, there is a significant decrease in the amount of time it takes for a generic product to be commercialised. These factors together can decrease the cost of the medicine when it reaches the market and help to lower overall healthcare costs while delivering high-quality topical products to patients that meet current regulatory standards.

The Intricacies of Demonstrating Topical Generic Product Bioequivalence to an Innovator/Reference Product

For a topical generic product to assume the safety and efficacy established by the innovator product, bioequivalence between both products must be demonstrated with the generic product being qualitatively (Q1) and quantitatively (Q2) the same as the reference product. The generic product must also establish the same quality and manufacturing standards as the reference product. For cases where the characterisation techniques of the reference product are now outdated, a higher standard must be met. Recently with the new draft guidance, there is an increasing focus on demonstrating extended pharmaceutical equivalence including matching the physical structure/microstructure and transformation upon application (Q3) of the reference innovator product within the generic. Such data was likely never submitted for the innovator product and is based upon



acceptable comparative physiochemical characterisation. This may involve extensive rheological characterisation and potentially an assessment of the drug in solution and suspension (e.g. particle size and distribution and polymorphic form) within the product and any changes of the product over its shelf life. These standards can be met through the use of *in vitro* testing.

With regards to the demonstration of bioequivalence, *in vitro* testing provides a series of valuable tools used to assess a product's performance as it relates to how the drug is released from the formulation, penetrates and/or permeates the epithelium, and/or engages the biological target. As such, *in vitro* models, often in combination with biological disease activity models, are vital for demonstrating the equivalence of product performance to regulatory standards.

In vitro release testing (IVRT) has been historically used throughout the topical development cycle to ensure the quality of a product is retained throughout its shelf life by measuring drug release over time from the dosage form. More recently, to support a claim of bioequivalence, IVRT methods are being developed and validated to more strict criteria to show with a high degree of confidence that the drug in the generic product has the same release characteristics as the reference product. IVRT has proven to be an invaluable tool for moderately complex products but does not provide any indication of how the formulation impacts the drug's absorption across the skin. Therefore, *in vitro* permeation/penetration testing (IVPT) must also be utilised to demonstrate bioequivalence for more complex topical dosage forms.

IVPT allows for the study of percutaneous absorption and determination of the pharmacokinetics (PK) of topically applied drugs. This *in vitro*/*ex vivo* model most commonly uses excised human tissue mounted in specially designed static or flow-through diffusion cells that allow the tissue to be maintained at a temperature and humidity that matches *in vivo* conditions. The formulations are applied to the surface of the skin and the permeation of the compound is measured in a receiver fluid underneath the tissue samples. It also allows the drug and metabolites within the different layers of the skin to be quantified. Both the rate of permeation (drug in receiver fluid) and levels of penetration (drug in skin layers) can be analysed and used to demonstrate equivalence. However, neither IVRT nor IVPT can demonstrate whether the drug that is moving into and through the skin is biologically active.

To demonstrate the biologic equivalence of the generic product and reference product for the treatment of skin infections, inflammatory skin diseases, or bacterial infections, *in vitro*/*ex vivo* disease or pharmacodynamic (PD) models are proving to be vital for derisking the approval process. It is now possible to keep the skin alive for several weeks while exposing it to different types of infections (bacteria, viral, fungi, etc) and/or stimulations (e.g. UV, inflammation, radiation, etc). The tissue can also be co-cultured with other cell types if they are not present in normal healthy tissue to create more complex mechanistic PD models. Disease activity models have the added advantage of allowing the drug to be

quantified in the tissue in combination with the PD activity to create a PK/PD analysis.

For now, the EMA/MHRA and the FDA guidances focus exclusively on IVRT and IVPT as an alternative to clinical studies with such disease models lacking comparative descriptions. However, these guidances continue to be discussed throughout the industry and scientific community mainly through workshops and public presentations. Along with the disease models, other techniques such as tape stripping and open flow microperfusion are also being advocated as tools for demonstrating bioequivalence.

Whatever the techniques involved, there has certainly been an underappreciation of the work required to meet these new standards, especially as the methods needed to be validated with current quality approaches. This volume of work comes with a cost and timeline that may have been originally underestimated.

With regards to the added tier of demonstrating extended pharmaceutical equivalence (Q3), there is much discussion about the relevance of characterising and comparing the generic and innovator topical products with regards to microstructure and its transformation when any such minor differences are unlikely to translate to differences in performance when assessing drug release (IVRT), permeation (IVPT) or a clinical assessment. Studies are also showing that long since approved innovator or reference products were inevitably not assessed with the level of rigor and quality standards applied to the generic product that is being developed 40-50 years later. As such, further advice is required with regards to what to do in this case. For example, would regulatory agencies allow modifications in the generic formulation composition to ensure its quality and performance (rheology, drug purity and release) are maintained for longer than the original approved shelf life. Would this simply be an improved generic or a hybrid and what would be required to demonstrate bioequivalence from the *in vitro* tests?

In addition, there are certainly some technical challenges associated with IVRT and IVPT when developed and validated with the higher standards that are now required. Skin donor variability is one of the major contributors and technical challenges associated with IVPT which can be compounded with older reference products where the drug is in suspension or partial suspension. Some of the other challenges for IVRT and IVPT are associated with the acceptance criteria and statistical analysis which differ between the FDA and EMA guidance meaning a generic company can develop a generic product of an innovator on the market in both the US and Europe which is approvable in the US only.

Conclusion

Although the bioequivalence guidance released are in draft and/or product-specific, the efforts made by regulatory authorities around the globe are very much appreciated by the generic industry and have had a noticeable impact on the development and approval of generic products.

The FDA continues to accept pre-ANDA meetings, and the EMA continues to use scientific advice meetings to provide product-specific guidance on the methodologies and protocols around demonstrating bioequivalence in topical generic products. The critical areas for which advice is given are the demonstration of sameness/equivalence between a topical reference product and a generic product—specifically, extended pharmaceutical equivalence and bioequivalence.

Regulatory bodies have also engaged industry leaders with each new guidance to ensure that the guidelines proposed by the regulatory authorities are consistent with industry standards and best practices. In 2021 and 2022, the FDA, in combination with the Center for Research on Complex Generics (CRCG), held free public workshops featuring presentations and discussions from industry leaders aimed at *in vitro* methods for demonstrating bioequivalence in complex generic products.

While the guidances are challenging and subject to continuous improvement, the cost reduction and process simplification associated with demonstrating bio-equivalence using *in vitro* methods only are beneficial for several reasons. Drug developers can enter generic markets with a significantly lower investment cost and shorter timeframe. Lowering those barriers to entry into the generic market enables governments to reduce healthcare costs more swiftly. This encourages further production of high-quality, affordable medicines made available to the general public.

Since the completion of this article, the FDA has released updated draft guidances for topical generic products.

REFERENCES

1. Evers P, "Skin Disease Treatment Technologies and Global Markets". BCC Research, Jan 2016.

Jon Lenn

Jon Lenn has direct responsibility for MedPharm's operations in the United States based out of Durham, North Carolina. 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 with Connetics, Stiefel and GSK and has been directly involved with the development and approval of 8 products. He received his PhD on the topical delivery of macromolecules from the University of Reading.

Marc Brown

Prof. Marc Brown co-founded MedPharm in August 1999. He has been the guiding force behind all of MedPharm's scientific developments and intellectual property. He has been Professor of Pharmaceutics in the School of Pharmacy, University of Hertfordshire since 2006 and has visiting/honorary professorships at the Universities of Reading and King's College London. He 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 over 55 products that are now on the market in Europe, America and Japan. Prior to MedPharm he was an academic in the Pharmacy Departments at King's College London (KCL) and the University of Hertfordshire. He retains honorary and visiting Professorships at the University of Reading, KCL, and De Montford University and in 2022 was awarded the status of Professor Emeritus of the University of Hertfordshire.