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Short communication

Challenges in the development and registration of generic topical products

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Introduction

Topical delivery of active substances is most widely used in the treatment of skin diseases. It offers advantages such as non-invasiveness, direct drug delivery at the site of action, patient compliance and lower cost of treatment.

The marketing authorization approval of a topical generic product until recently required evidence on therapeutic equivalence in relation to a reference product documented through clinical/pharmacodynamic endpoint studies. However, regulatory bodies have updated the regulation relevant to topical generic products and became open to accept new surrogate methods for topical bioequivalence assessment.

The Draft Guideline on quality and equivalence of topical products by European Medicines Agency (EMA) offers guidance on the quality of topical products, not covered by other general quality guidelines, when developing a generic topical product. The guideline clearly states that regulatory applications based in literature to demonstrate safety and efficacy should be supported by equivalence data of the formulation. At the same time, provides details of *in vivo* and *in vitro* models that may substitute clinical data and when biowaivers are applicable.

Regulatory aspects in obtaining and maintaining marketing authorization for generic topical drug product

Proving equivalence of generic topical drug products vs. reference medicinal product

Proving topical bioequivalence between a generic and reference medicinal product is a very complex process, which is basically dependent on the formulation of the product. The basis of the topical generic products development is, understandably, an in-depth characterization of the reference product. The Regulatory agencies, such as EMA and U.S. Food and Drug Administration (FDA), have improved the topical generic products development process by promoting the extended pharmaceutical equivalence concept. According to the draft EMA guideline, for simple formulations, bioequivalence may be demonstrated by documenting the qualitative (Q1), quantitative (Q2), microstructure (Q3) and performance (Q4) equivalence. Nevertheless, when addressing complex semisolids, equivalence regarding local availability should also be demonstrated which may be an extremely difficult and challenging goal. To optimize the regulatory requirements for the therapeutic equivalence of topical generic drug products, as the “one size fits all” approach will not work for BE determination of all types of topical dosage forms, the Strawman decision tree and the Topical Drug Classification system (TDS) are common features that facilitate product development, reduce the regulatory burden and assure product quality (Miranda et al., 2018).

Challenges in proving Q1, Q2, Q3 and Q4 equivalence

Since the qualitative composition of the comparator product is always included in the available product information documents, proving Q1 equivalence, seems to be relatively simple. However, matching the grades of the excipients used is an important rule for achieving the product performance and Q3 similarity. If the information of the grade is not available, analysis of different grades and relations with the product performance is considered beneficial however, it is a quite demanding process.

The approach for obtaining the Q2 equivalence is performance of reverse engineering of the comparator product, or to have information of the full qualitative and quantitative composition of the product via publicly

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available databases which is almost impossible to obtain, and it is recommended to be accompanied by the reverse engineering approach anyways. Another issue, beside the difficulties in acknowledgment of the quantitative composition of the comparator product is the patent pendings, variability of the excipients in their grades, batch-to-batch variabilities of the excipients or the unsatisfactory outcome of the reverse engineering leading to non-similarity in the surrogate tests. Therefore, accomplishing the Q1/Q2 equivalence could be a quite challenging task (Shah, et al., 2016).

The IVR (in-vitro release) (Q3) reflects the microstructural arrangement of the dosage form and the state of aggregation of dispersed particles. Q3 mainly follows and it depends on the success of the Q1 and Q2 sameness and reflects the similarity in the in-vitro release between the generic and the reference product. The *in vitro* release characteristics of the drug from its dosage form is an excellent indicator that enables identifying the microstructural arrangement of the dosage form. However, there are cases where even with successful Q1, Q2 and even Q4 sameness, Q3 equivalence was not achieved. Therefore, it remains unclearly defined in the guidelines whether some rheology endpoints can be waived or if there are some acceptable and completely safe criteria for the patients or if there are additional bridging data that could mitigate this (Miranda et al., 2022).

Q4 (performance) equivalence challenges arise mainly from the established criteria in the EMA guideline, which are very demanding. Even when no clinically significant difference is obtained, the strict criteria in the guideline may lead to a conclusion that there is no Q4 equivalence between the test and the reference product not considering the intrinsic variability of topical semisolid dosage forms. With regards to Q5 similarity (equivalence with respect to efficacy), additional challenge is the condition in each IVPT (In vitro permeation testing) 12 donors with at least 2 sections per donor to be used, due to the inter- and intra-individual variability of human skin. This significant increase in the requirements compared to the pre-existent guidelines could be extremely difficult since human skin is usually retrieved from plastic surgery, with ethical consent being required. (Shin, et al., 2020).

Post-authorization changes

For any change during the life-cycle of the product, a risk assessment should be performed to determine its impact on quality, safety, or efficacy of the product. The guideline states that if the proposed change does not meet the extended pharmaceutical equivalence acceptance criteria, or qualitative and quantitative composition, then equivalence should be demonstrated using an appropriate clinical study. Description of different situations and exceptions where waivers in respect to post-authorization changes are applicable, as well as inclusion of the possibility of measuring equivalence by other physical and chemical means than IVRT (in cases where IVRT is not discriminative) are not very clearly stated. Due to the lack of experience and close recommendations in the guideline post-authorization changes remain a big challenge for the topical generic products.

Conclusion

The EMA guideline on quality and equivalence of topical products following the FDA approach for topical products is a refreshment for the pharmaceutical industry, since it promotes a valuable input on the standardization and definition of strict criteria regarding the definition, as well as validation of the extended pharmaceutical equivalence. However, the presented approach by EMA also bears some relevant limitations which should be carefully debated in a near future in order to allow a successful translation into the practice. Sufficient and clear guidance available to the industry, will lead to a facilitated development and registration of a generic topical product, still maintaining the ultimate requirements for high quality, safety and efficacy, and finally their availability to patients and consumers at a more reasonable cost.

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US FDA Product-Specific Guidances for Generic Drug Development.