

Unique Challenges for Topical Drug ANDA Submission

Topical drugs, commonly applied to the skin for local therapeutic effects, play a crucial role in the treatment of various dermatological conditions. When seeking approval for generic topical drugs, pharmaceutical companies are required to submit an Abbreviated New Drug Application (ANDA) to the U.S. Food and Drug Administration (FDA). This application necessitates quality compliance with specific testing requirements that are unique to topical formulations. This white paper explores the distinctive challenges involved in the development and submission of topical drugs for FDA ANDA approvals.



Some of the distinctive challenges involved in the development and submission of topical drugs for FDA ANDA approvals include:

Comparative physicochemical & structural (Q3) characterization

Topical generic drug products submitted in ANDAs require rigorous Q3 characterization tests to demonstrate their quality, performance, and equivalence to the reference listed drug. The formulation's appearance, pH, viscosity, rheological behavior, microscopy, particle size analysis, crystal morphology and consistency are critical factors that affect product performance and patient acceptability. A thorough assessment of these properties is necessary to ensure consistency with the Reference Listed Drug (RLD). Furthermore, the identification and quantification of active and inactive ingredients, including potential impurities, are crucial to assess the drug's quality and safety. For example, a comparative Q3 characterization study may involve analyzing the rheological properties of a generic topical gel and comparing it to the RLD to ensure similar consistency and spreadability.



Performance testing (in vitro release & permeation testing)

In Vitro Release Testing (IVRT) serves as a pivotal parameter in the evaluation of topical drug products. It measures the rate of drug release and extent of drug release from the formulation through a suitable surrogate membrane. IVRT is crucial for establishing the bioequivalence of generic topical drugs, ensuring that they release the drug in a similar manner as the RLD. In Vitro Permeation Testing (IVPT) evaluates the permeation profile of topical drug products and provides bioavailability of drugs at the site of interest. This test assesses factors such as drug release cutaneous kinetics, permeation, and skin penetration. Additionally, studies may include comparisons of release profiles under various conditions, such as different vehicles or application sites. IVPT flux profiles resemble pharmacokinetic drug profiles, so specific IVPT endpoint studies can be designed to mimic maximum concentration (C_{max}) and Area Under the Curve (AUC) concentration-time. IVPT & IVRT BE studies that are submitted in ANDA's go through rigorous development, validation, and quality system requirements to show equivalence to the Reference Listed Drug (RLD).

Skin irritation and sensitization studies

Topical drugs must undergo rigorous testing to evaluate their potential for causing skin irritation and sensitization. These studies are essential to ensure patient safety. Skin irritation tests assess the potential for localized adverse effects, such as erythema, edema, and other signs of inflammation. Sensitization studies, on the other hand, aim to identify potential allergenicity by determining if a substance can induce an allergic response in susceptible individuals. These assessments involve in vitro tests, such as the human repeat insult patch test (HRIPT), and in vivo tests, including the guinea pig maximization test (GPMT) and the murine Local Lymph Node Assay (LLNA).

Common deficiencies



FDA reviews have identified common deficiencies in Q3 characterization, IVRT, and IVPT studies for topical generic drug products. These deficiencies include inadequate study design, incomplete data, inadequate quality system controls, or failure to demonstrate equivalence. Addressing these deficiencies is critical. For example, ensuring comprehensive data collection and analysis, selecting appropriate study designs, and using validated methodologies can help mitigate common deficiencies.

Practical considerations

When conducting these kinds of tests when developing topical generics, practical considerations should be taken into account. These include selecting suitable test methods, investing ample development time, establishing relevant acceptance criteria, and ensuring the reliability and reproducibility of results. For instance, selecting a validated analytical method to assess the active ingredient content in a topical generic product can enhance accuracy and reproducibility.



Packaging considerations

Topical drugs often require specialized packaging to maintain stability, integrity, and user convenience. Choosing appropriate packaging materials and formats is crucial. For example, selecting an airless pump container for a topical emulsion to prevent oxidation and maintain product potency can be a packaging consideration. Additionally, the container closure system, including the packaging material and the drug's interaction with the container, must be thoroughly evaluated. Compatibility studies assess the drug's stability and potential interactions with the container, ensuring that the drug remains safe, effective, and unchanged throughout its shelf-life.

Stability and shelf-life



Topical drugs undergo various environmental conditions during storage and use, necessitating stability testing. This involves assessing product stability under different storage conditions, container closure systems, and determining appropriate expiry date. For instance, conducting accelerated stability studies to evaluate the shelf-life of a generic topical ointment can provide valuable insights into its stability under stress conditions.

Regulatory requirements

Topical drug ANDA submissions must comply with FDA regulatory guidelines, GMP, and stringent quality control standards. Navigating these requirements is essential for successful submissions. For instance, ensuring adherence to FDA guidelines on manufacturing practices and quality control during the production of a topical generic product is crucial for regulatory compliance.

Patent and intellectual property considerations

Navigating patent landscapes is crucial for topical drug ANDA submissions. Identifying potential patent challenges and developing strategies to address them is essential. For example, conducting a thorough patent search and ensuring compliance with intellectual property laws can help mitigate patent-related issues during the submission process.

In conclusion, developing and submitting a generic topical drug for FDA ANDA approval requires meeting specific testing requirements that have unique challenges for development and manufacturing teams. Physico-chemical property evaluation, in vitro release testing, skin irritation and sensitization studies, stability assessment, and container closure system evaluation are all vital components of this process. Compliance with these unique requirements ensures the safety, efficacy, and bioequivalence of topical drugs, facilitating their approval and availability to patients.





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