

Advisory Committee for Pharmaceutical Science Meeting October 21 - 22, 2003

Topic: Research for Generics - Bioequivalence of Topical Products

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Bioequivalence of Topical Products

Problem Statement

Despite tremendous efforts by industry, FDA, and academia for the past decade, a cost-effective, scientifically sound system to evaluate the therapeutic equivalence of topical products is still unavailable. For example, the bioequivalence demonstration of many topical products relies on clinical trials that may require hundreds of patients (due to high variability of the patient population). These studies can also require a long time and complex statistical analysis. All these factors combine to render the study design expensive. Due to the limited knowledge and experience of sponsors, these costly studies may have to be repeated to meet the confidence interval criteria to demonstrate bioequivalence. The lack of a bioequivalence method has limited the availability of generic products as well as the ability of innovator companies to make post-approval formulation or process changes.

Background

The agency has been evaluating topical product equivalence issues using Dermatopharmacokinetic (DPK) techniques such as skin-stripping for more than a decade. In 1998, the agency issued a draft Guidance for Industry titled "*Topical Dermatological Drug Product NDA's and ANDA's—In Vivo Bioavailability, Bioequivalence and In Vitro Release*". Subsequently in 2000, two definitive equivalence studies were conducted in humans using tretinoin gel 0.25%, based on the skin-stripping methodology described in the Guidance. The studies were conducted at two different locations by two expert researchers: Dr. Lynn Pershing of the University of Utah and Dr. Tom Franz, of 'Dermtech Inc.'. In addition, in the year 2001, the Agency also conducted a pilot equivalence study in one subject using three tretinoin gel 0.25%, formulations. In an Advisory Committee meeting held on November 21, 2001, the study results were discussed and the committee concluded that the skin-stripping technique resulted in non-reproducible results for the tretinoin gel Avita product; the draft Guidance was therefore withdrawn.

The Committee also expressed concern that the guidance covered all topical products including those that are delivered to areas of skin without healthy stratum corneum (SC). For drugs treating target sites that are not the SC, the DPK method may not accurately reflect therapeutic effectiveness if penetration through another pathway (e.g., hair follicles) is important. Similarly, because healthy SC is absent in many skin diseases, therapeutic effectiveness could be unrelated to SC penetration.

At the March 12, 2003 advisory committee meeting FDA discussed the classification of topical products. The committee indicated the importance of physical characterization of topical products.

To move forward the FDA is working to develop improved DPK methods for a focused product class (topical anti-fungals) and to design a framework for physical characterization of topical products.

Improved Dermatopharmacokinetic methods

To develop an improved DPK method FDA is first considering topical anti-fungal products. These products target the stratum corneum itself, thus skin-stripping directly measures the delivery of the drug to its site of action. Experience from these products can then be generalized to other topical products.

Some of the problems with the previous skin stripping trials have been identified. The withdrawn guidance mandated removing the same number of strips from each subject irrespective of the amount of stratum corneum removed. However both the thickness of the stratum corneum and the amount of skin removed by each strip varies between individuals and so each individual would have a different and uncontrolled fraction of the stratum corneum removed. Mathematical modeling shows that removing the same fraction of the stratum corneum from each individual is important for reproducible measurement. The withdrawn guidance was not specific about the protocol for drug application and stripping and it is likely that different control of the drug application area and stripping area contributed to the contradictory results observed in the past.

In the new method there will be precise specification of the drug application area and stripping area. The thickness of the stratum corneum and the thickness removed will be measured so that for each subject it is assured that a sufficient fraction of the stratum corneum has been removed. Mathematical modeling of diffusion through the stratum corneum will allow the choice of application strategies and stripping times to minimize variability in the method.

Introduction to the Q3 concept

Working Definition of the Q3 concept: Q1 means qualitative similarity between generic and reference listed products, while Q2 represents quantitative similarity of composition. Q3 is a newly defined term that describes structural similarity and refers to the arrangement of matter and state of aggregation of the product. Examples of products that are Q1 and Q2 similar to each other, but differ in Q3 would be a solid dosage forms that differ only in crystal structure or suspensions or emulsions that differ only in particle size distribution or gels that differ only in the extent of cross-linking.

For pharmaceutical dosage forms that are in thermodynamic equilibrium,

such as solutions of small molecules, specification of Q2 and the conditions of temperature and pressure uniquely determine Q3. For the many dosage forms that are not in thermodynamic equilibrium, including most topical formulations, their Q3 or arrangement of matter depends on their history which includes the manufacturing processes and the conditions of storage. Differences in Q3 could manifest themselves as differences in physical properties such as rheology or in dissolution rate.

Historically, for solid oral dosage forms FDA has not been concerned with Q3 identity because in vivo bioequivalence methods were readily available. For example, two tablet formulations that have different particle sizes but still provide the same rate and extent of drug delivery to the blood would be considered bioequivalent even though they were not Q3 to each other. Where the Q3 concept is especially important is for products that are locally acting and do not have demonstrated in vivo bioequivalence methods such as topical products.

For topical products FDA is investigating how to characterize Q3 for different dosage forms and how to demonstrate the validity of Q3 to bioequivalence determinations.

Measurement of Q3: The nomenclature for topical products is confusing as discussed at a previous advisory committee meeting. An FDA working group is developing an improved classification tree that defines the different dosage forms (suspension, lotion, paste, gel, cream, ointment) based on measurable physical properties. The appropriate Q3 methods would be different for each category of products and it would be designed for the specific physical chemistry in each dosage form.

FDA envisions that the primary Q3 characterization of topical dosage forms would be determination of particle/droplet size distributions and characterization of the rheology. The size distribution would directly indicate the distribution of matter, while the rheology is very sensitive to how the dispersed material interacts with each other. As an example two suspensions with the same particle size distribution may have vastly different rheology if the surface chemistry of the particles is not identical. Rheological characterizations should not be limited to the viscosity alone but should recognize that most topical dosage forms are non-Newtonian (viscosity depends on shear rate) and may also possess yield stresses (the material is solid-like or liquid-like depending on the applied stress). The rheological data that should be supplied for both products being compared is a plot of shear stress versus strain rate, a plot of the linear viscoelastic response (G' and G'' versus frequency), and a determination of the yield stress. The stress-strain plot will indicate the degree of non-Newtonian behavior present, linear viscoelasticity will characterize the relaxation times of the material, and the yield stress is part of the distinction between different dosage forms.

An important issue in the characterization of Q3 is to recognize that methods to measure the particle size distribution often involve modification of the product (dilution to use dynamic light scattering or evaporation of solvent to use microscopy). While these issues do not limit characterization by the product manufacturers, for the comparison of generic and innovator products only the final innovator product is available. There is concern that

modification of the product will invalidate the particle size measurement, thus FDA is interested in methods for particle size determination that can be used in situ.

Q3 validation: Q3 must be demonstrated to be related to therapeutic equivalence of generic topical products. Existing markers such as drug release can be used to verify the Q3 identity is associated with drug product performance. Techniques of drug release using different apparatus and methods will be evaluated for this role. Improved DPK methods could also serve to validate the role of Q3. It will also be valuable to identify critical manufacturing variables that are associated with variation in Q3.

Questions for the Committee:

DPK

What type of studies should be conducted to validate the DPK method?

Q3

What type of data is needed to demonstrate that two products are Q3 equivalent?

How should the Q3 concept be validated or demonstrated?

- Demonstration that we can detect changes in manufacturing processes?
- Demonstration that we can detect formulations with known differences?
- Demonstration that drug release rates are identical?

Bioequivalence for topical products

What role should Q3 and DPK play in the demonstration of bioequivalence for topical products?

- Under what circumstances should Q3 equivalence be sufficient to justify a waiver of in vivo bioequivalence tests?
- Under what circumstances should Q3 equivalence and a DPK method in healthy subjects be sufficient to determine bioequivalence?