Bioequivalence recommendations for tretinoin-containing topical products

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Mengmeng Niu, Markham C. Luke, and Priyanka Ghosh

Division of Therapeutic Performance I, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, 20993

CONTACT INFORMATION: Mengmeng.niu@fda.hhs.gov

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PURPOSE

In 1971, tretinoin topical solution and swab, 0.05% were approved under new drug application (NDA) 016921 as the first retinoid topical product for the treatment of acne vulgaris by the U.S. Food and Drug Administration (FDA). Since then, topical tretinoin, either alone or in combination with benzoyl peroxide, clindamycin phosphate, etc., have been approved in various dosage forms including solution, gels, creams, and lotion. Formulations containing microparticles suspended in the gels and creams, thus leading to additional complexity, have also been utilized to deliver tretinoin. Based on the complexity of the microstructure of these tretinoin-containing topical dosage forms, among other factors, FDA has recommended various approaches for establishing bioequivalence (BE) of prospective generic tretinoin-containing topical products. The purpose of the current work is to provide a comprehensive review of the microstructural complexity of tretinoin-containing topical products and the development of science-based BE approaches recommended in the FDA's product-specific guidances (PSGs).

METHOD(S)

Based on the complexity of the microstructure, tretinoin-containing topical products were categorized as single-phase, conventional multiphasic and complex multiphasic systems in this work. The relationship between a product's microstructural complexity and the recommended BE approaches obtained from the FDA's published PSGs were reviewed for 17 tretinoin-containing topical reference listed drug (RLD) and reference standard (RS) products. Trend analysis was conducted on the components of the BE approaches recommended for these products. Additionally, research was conducted to understand the relationship between a drug product's microstructure and performance to support the development of a waiver of in vivo BE studies for intermediate strengths of tretinoin (microsphere-based) topical gel.

Approaches utilized for establishing BE for approved ANDAs and in-house pending ANDAs of tretinoin-containing topical products were also analyzed based on the products' structural complexity.

DISCLAIMERS

This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.

RESULT(S)

As of 09/09/2024, there are 19 approved RLDs for tretinoin-containing topical products. Among the 19 products, 17 have published PSGs. Comparative clinical endpoint (CCEP) BE studies have been recommended in all 17 PSGs. At this time efficient characterization-based approaches have been recommended for single-phase systems (e.g., tretinoin topical gels), but not for the conventional multiphasic (e.g., tretinoin creams and lotions) or complex multiphasic (e.g., tretinoin gels containing microparticles) systems. As a component of the characterization-based BE approaches, as the structural complexity increases, additional physicochemical and structural (Q3) tests may be recommended. For example, compared to single phase tretinoin topical gels, characterization of globule size distribution and other tests may be relevant for multiphasic tretinoin topical creams and lotions. For more complex multiphasic systems, such as Retin-A micro (tretinoin) topical gel, Generic Drug User Fee Amendments (GDUFA)-funded research demonstrated that a microparticle's morphology, particle size, spatial distribution of tretinoin and the interaction of tretinoin with polymer matrix play an important role in controlling drug release which may in-turn affect tretinoin bioavailability. An analysis of the approved and pending ANDAs for tretinoin-containing topical semi-solid products indicates that, in the recent past, an increased number of ANDAs utilized characterization-based BE approaches.

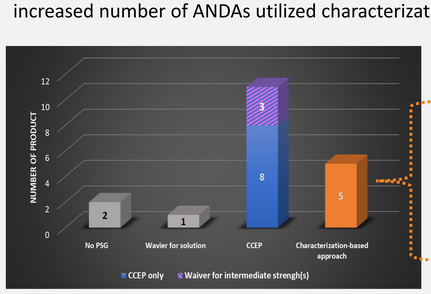

Figure 1: PSG recommendations for tretinoin-containing topical products (data till 09/09/2024). *Five of the 19 (26.3%) tretinoin-containing topical RLD/RS products contain* efficient characterization-based approaches. *Eleven of the 19 contain CCEP, however, 3 of the 11 also have a waiver of CCEP option for the intermediate strength(s).*

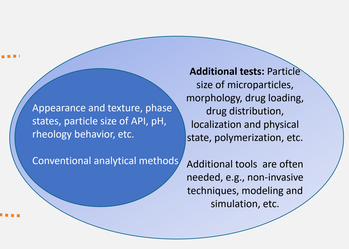

Figure 2: GDUFA research revealed that as the structural complexity increases, additional Q3 tests and additional tools may be needed for tretinoin-containing topical products. *Related publication: Physicochemical and structural evaluation of microparticles in tretinoin topical gels. Int J Pharm. 2022 May 25:620:121748.*

System	Single-phase system	Conventional multiphasic system	Complex multiphasic system
Phase	One phase (e.g., aqueous phase, or alcohol phase)	W/O; O/W	Microparticles in a semi-solid dosage form
Dosage form examples	Gel, suspension, solution	Cream, lotion	Microsphere-based topical gel
Typical BE Approaches in other PSGs	CCEP, VC, Characterization-based BE approach, waiver of in vivo BE studies	CCEP, VC, Characterization-based BE approach	CCEP
Tretinoin product examples	Retin-A (tretinoin) topical gel	Retin-A (tretinoin) topical cream	Retin-A Micro (tretinoin) topical gel
Approaches in PSGs for tretinoin products	CCEP and Characterization-based BE approach	CCEP and waiver of CCEP for intermediate strength(s)	CCEP and waiver of CCEP for intermediate strength(s)
Characterization-based BE approach for tretinoin products	No significant difference in formulation/Q3/IVRT	Challenging due to lack of appropriate method for characterization of cutaneous pharmacokinetics (PK) of tretinoin	Challenging due to lack of appropriate method for characterization of cutaneous PK of tretinoin

Table 1: Based on the complexity of the microstructure, tretinoin-containing topical products were categorized as single-phase, conventional multiphasic and complex multiphasic systems in this work. A brief overview of the BE recommendations are listed in the table for topical products in general and tretinoin-containing topical products based on the structural complexity. *VC: vasoconstrictor study; W/O: water in oil; O/W: oil in water; IVRT: in vitro release test; IVPT: in vitro permeation test*

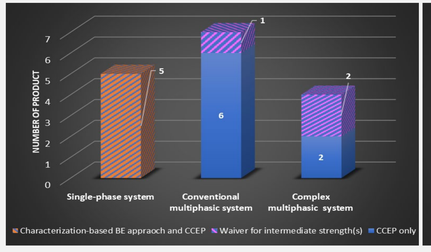

Figure 3: BE approaches recommended for tretinoin-containing topical semi-solid products with different structural complexity. *Even though CCEP BE study is still the dominant study recommended for tretinoin-containing topical products, as of 09/09/2024, efficient characterization-based approaches have been recommended for single-phase systems (e.g., tretinoin topical gels), and waiver for the intermediate strength(s) have been recommended for the conventional multiphasic (e.g., tretinoin creams) and complex multiphasic (e.g., tretinoin gels containing microparticles) systems.*

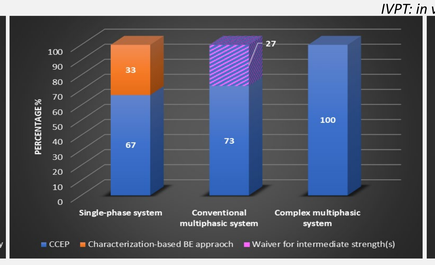

Figure 4: Approaches for establishing BE used to support approved ANDAs of tretinoin-containing topical semi-solid products. *As of 09/09/2024, 33% of the approved ANDAs established BE by using efficient characterization-based approaches for the single-phase systems; 27% ANDAs utilized a waiver approach for the intermediate strength for conventional multiphasic systems. For complex multiphasic systems, all ANDAs established BE using CCEP BE studies.*

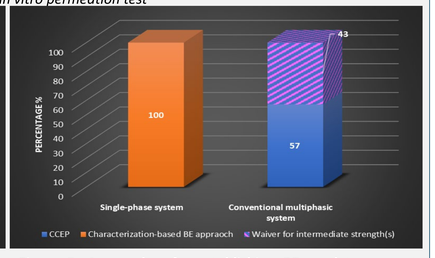

Figure 5: Approaches for establishing BE used to support pending ANDAs of tretinoin-containing topical semi-solid products. *As of 09/09/2024, all the in-house pending ANDAs since GDUFA II proposed to establish BE using efficient characterization-based approaches for the single-phase systems; 43% ANDAs proposed a waiver approach for the intermediate strength(s) of conventional multiphasic systems.*

RESULT(S)

As a separate matter, for tretinoin-containing topical products that are available in multiple strengths, the release of tretinoin from the drug product is expected to be proportional to the product strength. Waiver of in vivo studies for intermediate strength(s) of tretinoin-containing topical products have been recommended for conventional multiphasic tretinoin products (i.e., products referencing Retin-A cream) and complex multiphasic tretinoin products (i.e., products referencing Retin-A Micro gel, 0.06% and 0.08%).

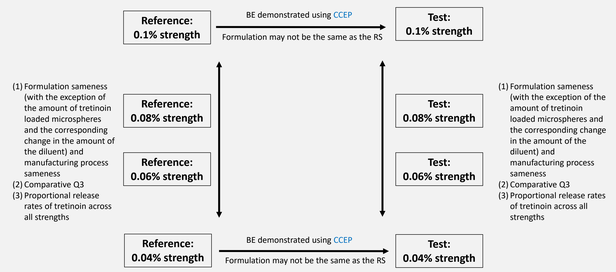

Figure 6: An outline of a waiver approach for complex multiphasic systems of tretinoin-containing topical products. *FDA revised the PSG for tretinoin (microsphere-based) topical gel in May 2024 to include a waiver of in vivo BE studies for the intermediate strengths (0.06% and 0.08%). Related publication: Understanding the impact of formulation design on microstructure and drug release from porous microparticle-based tretinoin topical gels. Int J Pharm. 2024 Mar 25:653:123794*

CONCLUSION(S)

In addition to CCEP BE studies, characterization-based BE approaches are designed based on the microstructural complexity of the drug products, supported by scientific research on the drug products Q3 characteristics and performance. GDUFA-funded research demonstrated that the microstructure of tretinoin-containing topical products such as rheology, globule size, etc., may impact the release of tretinoin from the drug products, and thereby the bioavailability. Therefore, the formulation and the microstructural properties for a given formulation are carefully considered during the development of BE approaches. Ultimately, available efficient characterization-based BE approaches and the waiver approaches for intermediate strength(s), in addition to the CCEP BE studies, are anticipated to streamline generic product development.

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