Enhanced Understanding of Structure Performance Relationship Using Modeling and Simulation- A Case Study with Dapsone Topical Gel

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Introduction

The previous product-specific guidances (PSGs) on dapsone topical gel for both strengths (7.5% and 5%) each recommended two options to demonstrate BE between a test product and the reference standard (RS): Option 1 is for a test product that has no difference relative to the RS in inactive ingredient components or composition, or in other aspects of the formulation (e.g., physicochemical and structural (Q3) attributes) that may significantly affect the local or systemic bioavailability (BA); it is a characterization-based bioequivalence (BE) approach that involves an in vitro release test (IVRT) BE study, an in vitro permeation test (IVPT) BE study, a BE study with pharmacokinetic (PK) endpoints, and other product characterization tests. Option 2 is a comparative clinical endpoint BE study.

In the dapsone topical gels, 7.5% and 5%, dapsone is partially dispersed in the formulation. The recommendations in draft PSGs for other single-phase topical gel products (irrespective of the physical state of the active pharmaceutical ingredient in the formulation, completely dissolved or dispersed), reflect that the risks associated with potential failures modes for BE with a test product compared to the RS are adequately mitigated by demonstrations of no significant difference in formulation components and composition, Q3 sameness, and an equivalent drug release rate using a validated IVRT method, without direct assessments of local and systemic BA from IVPT and in vivo PK BE studies, respectively.

The goal of the current work was to utilize a model-based approach to understand impact of Q3 attributes of dapsone gel on local and systemic BA following topical application of the drug product to determine whether evidence from direct assessments of local and systemic BA from IVPT and in vivo PK BE studies are necessary for BE recommendations for test products that meet the criteria for no significant difference in components or composition.

Materials and Methods

Dermal physiologically based pharmacokinetic (PBPK) models were developed for the prospective generic (test) product and the RS for approved abbreviated new drug applications (ANDAs). To inform drug product specific model parameters, the Q3 characterization data corresponding to the RS and test products were utilized. The developed models were validated (internal and external validation) using in vivo PK data from the in vivo BE studies with PK endpoints and IVPT data. To improve model performance, dapsone uptake from the drug product vehicle to the upper stratum corneum (SC) layer was optimized against observed data for ANDA 1 [Figure 1(a)].

The validated models were utilized to predict dapsone BA locally in the skin and in the plasma of virtual healthy subjects and assess BE in the SC, dermis and the plasma between the test product and the RS. The virtual BE (VBE) trials performed mirrored the pivotal in vivo BE studies with PK endpoints that supported the ANDA submissions in terms of the participating population, drug application conditions and dosage. Bioequivalence was determined by applying the same statistical analysis as the one implemented in the ANDAs.

Additionally, the validated dermal PBPK model for dapsone gel was utilized to identify Q3 characteristics that may impact local and systemic BA (sensitivity analysis). An overview of the overall workflow is captured on Figure 1.

The Multi-phase, multi-layer Mechanistic Dermal Absorption model in the Simcyp Simulator V22 (Certara, NJ) was utilized for model building and the VBE Module in Simcyp was utilized for the VBE assessments.

Dermal PBPK Modeling Supporting Updated BE Recommendations for Dapsone Topical Gels

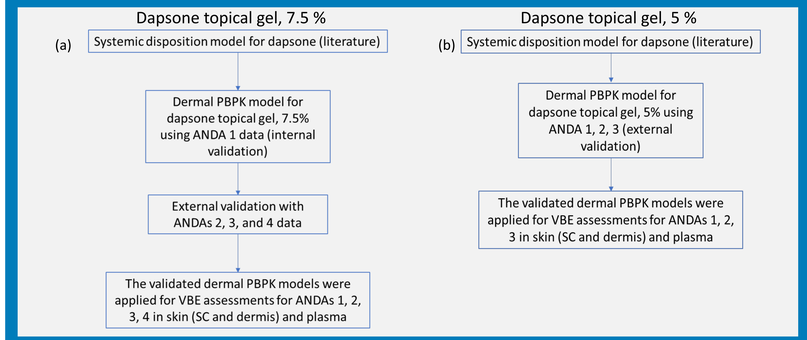
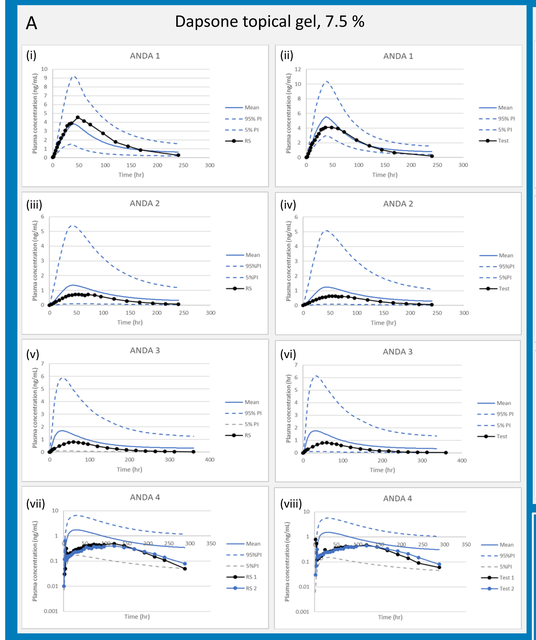


Figure 1. Overall workflow on model development, validation and application of dermal PBPK models for dapsone topical gel, 7.5% (a) and dapsone topical gel, 5% (b).



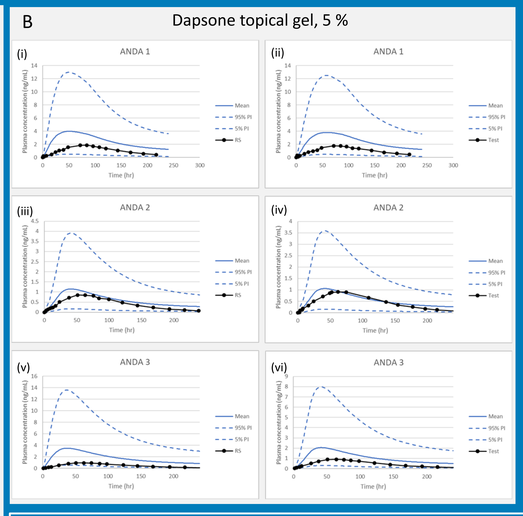


Figure 2. Observed (black and blue lines) versus predicted (blue solid line is mean and blue interrupted lines are 5 and 95% prediction intervals) mean PK profile of dapsone plasma concentration versus time following topical administration of the RS [(i), (iii), (v), (vii)] and test product [(ii), (iv), (vi), (viii)] within the scope of the pivotal in vivo BE study with PK endpoints supporting approved ANDAs 1-4 for dapsone topical gel, 7.5% (A) and approved ANDAs 1-3 for dapsone topical gel, 5% (B).

Table 1. Outcomes for VBE assessments performed using the developed dermal PBPK models (Figure 1). The virtual BE studies replicated the pivotal in vivo BE studies. Pass: Meeting BE criteria of 0.8 to 1.25. *The VBE analysis revealed dependency of the VBE outcome on particle size distribution and apparent viscosity and their interplay.

	Dapsone topical gel, 7.5%				Dapsone topical gel, 5%		
	ANDA 1	ANDA 2	ANDA 3	ANDA 4	ANDA 1	ANDA 2	ANDA 3
Matrix	VBE outcome						
SC	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Dermis	Pass*	Pass	Pass*	Pass	Pass	Pass	Pass*
Plasma	Pass*	Pass	Pass	Pass	Pass	Pass	Pass*

Results and Discussion

Dermal PBPK models for dapsone topical gels 7.5% and 5% were validated against in vivo PK data from approved ANDAs (Figure 2). These models were utilized to assess the impact of Q3 quality attributes on local and systemic bioavailability and showed that apparent viscosity, and particle size distribution for the undissolved dapsone in the gel, were formulation attributes that may impact the in vivo performance. The application of these models towards VBE assessments demonstrated that when the test product and the RS are Q3 the same, especially with respect to apparent viscosity and particle size distribution, they are found to be bioequivalent in the plasma within the scope of a VBE assessment, in accordance with the outcome of the in vivo BE study with PK endpoints (Table 1).

By leveraging the capability of dermal PBPK models to predict dapsone exposure not only in the plasma (systemic circulation), but also in the different skin layers, the virtual BE assessments showed that for all ANDAs where a VBE was performed, the test product and RS, when Q3 the same, were found to be bioequivalent in the stratum corneum and the dermis. These results are limited to test products that meet the criteria for no significant difference in components or composition, as specified in the aforementioned draft PSGs for dapsone topical gels.

Conclusions

The enhanced understanding of the structure-performance relationship of single-phase dapsone gels gained through the PBPK modeling research reported here, provides new insights that substantially minimize the risk of potential differences in local or systemic BA for dapsone topical gel test products that meet the criteria for no significant difference in components and composition relative to the RS, and which establish Q3 sameness compared to the RS, such that evidence from an IVRT BE study may be sufficient to mitigate the actual risks of failure modes for BE with these dapsone gels.

The compelling evidence from this PBPK modeling aligns with, and reinforces, the BE recommendations in the aforementioned draft PSGs for other topical gels and illustrates that those recommendations are also suitable for these dapsone topical gels, without additional evidence from direct assessments of local and systemic BA from IVPT and in vivo PK BE studies, respectively. The PSGs for dapsone topical gels were revised in February 2024 to remove IVPT and in vivo PK BE studies under Option 1[1,2], which reflects the Agency's current thinking. Apparent viscosity and particle size distribution appear to be Q3 quality attributes that may impact the local and systemic bioavailability of dapsone following application of dapsone topical gels, 7.5% and 5%.

References

1. Draft Guidance on Dapsone (topical gel, 7.5%), recommended Oct 2017; Revised Nov 2018, Nov 2019, Oct 2022, Feb 2024 available at https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_207154.pdf
2. Draft Guidance on Dapsone (topical gel, 5%), recommended Dec 2014; Revised Oct 2017, Nov 2018, Nov 2019, Oct 2022, Feb 2024 available at https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021794.pdf

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