Review Article

Theme: Pharmacokinetics, Biopharmaceutics and Bioequivalence: History and Perspectives

Guest Editors: Marilyn Martinez and Lawrence Yu

Survey of International Regulatory Bioequivalence Recommendations for Approval of Generic Topical Dermatological Drug Products

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Abstract. The objective of this article is to discuss the similarities and differences in accepted bioequivalence (BE) approaches for generic topical dermatological drug products between international regulatory authorities and organizations. These drug products are locally applied and not intended for systemic absorption. Therefore, the BE approaches which serve as surrogates to establish safety and efficacy for topical dosage forms tend to differ from the traditional solid oral dosage forms. We focused on 15 different international jurisdictions and organizations that currently participate in the International Generic Drug Regulators Pilot Project. These are Australia, Brazil, Canada, China, Chinese Taipei, the European Medicines Association (EMA), Japan, Mexico, New Zealand, Singapore (a member of the Association of Southeast Asian Nations), South Africa, South Korea, Switzerland, the USA and the World Health Organization (WHO). Upon evaluation, we observed that currently only Canada, the EMA, Japan, and the USA have specific guidance documents for topical drug products. Across all jurisdictions and organizations, the three approaches consistently required are (1) BE studies with clinical endpoints for most topical drug products; (2) *in vivo* pharmacodynamic studies, in particular the vasoconstrictor assay for topical corticosteroids; and (3) waivers from BE study requirements for topical solutions. Japan, South Africa, the USA, and the WHO are also making strides to accept other BE approaches such as *in vivo* pharmacokinetic studies for BE assessment, *in vivo* dermatopharmacokinetic studies and/or BE studies with *in vitro* endpoints.

KEY WORDS: bioequivalence; bioequivalence studies with clinical endpoints; biowaivers; dermatopharmacokinetics; topical dermatological drug products; vasoconstrictor assay.

INTRODUCTION

Recommendations for successfully developing generic drug products that will meet regulatory agency requirements for marketing approval can be found in the guidance's for industry, as well as in individual agency policies and regulations. Globally, the regulatory approval process for generic locally acting topical dermatological drug products has often been hampered. This is due to the limited number of acceptable approaches that are suitable to demonstrate bioavailability (BA) and bioequivalence (BE) between a proposed generic (multisource) product and innovator

(reference) product. This is a major issue for the generic pharmaceutical industry and regulators. Three critical factors in BE assessment of topical dermatological drug products are (1) the site of activity, (2) varying therapeutic drug classes, and (3) multiple dosage forms varying from simple to complex (1–3). The site of action for topical dermatological drug products is commonly on the surface of the skin (stratum corneum) for local action and direct therapeutic effect.

The therapeutic drug classes mainly include analgesics, anesthetics, antibacterials, antifungals, anti-inflammatory (non-steroidal), antimitotics, antivirals, glucocorticoids (corticosteroids), oncologics, and retinoids. The drug can be applied to various areas of the skin such as the face, arm, leg, scalp, hand, and/or foot. The site of application is dependent upon the skin disease and/or disorder state. The multiple dosage forms range from solutions to semi-solids, such as creams, foams, gels, lotions, ointments, pastes, solutions (aqueous or oily), and sprays (4). These differences in dosage forms and differences in vehicles can have a direct impact on drug absorption and thus efficacy of the drug product. The therapeutic effect elicited by a topical dermatological drug product is based on a sequential process (3,5,6). The process is as follows: (1) release of the drug from the vehicle, (2) penetration/diffusion of the drug through the skin,

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(3) activation of the desired therapeutic effect, and (4) sustaining a therapeutic level in the target tissue for a sufficient duration of time to elicit the desired therapeutic effect. The extent of drug absorption is dependent on the interaction between the drug, vehicle, and the skin. This interaction controls partitioning into and diffusion through the stratum corneum, the outer-most layer of the skin, along with the site of activity and the skin disease and/or disorder state.

In general, topical dermatological drug products are not intended for systemic absorption. Therefore, the utilization of *in vivo* pharmacokinetic (PK) studies, an established approach for BE assessment of solid oral dosage forms, is often not appropriate for topical dosage forms. Often, even when a topical dermatological drug product is systemically absorbed, there is no established link between the concentration of the drug in the systemic circulation and the therapeutic effect. The only link that can generally be made is to the adverse event(s) that may occur due to systemic absorption. In some cases, systemic absorption may occur due to the site of action being the underlying levels of the skin, such as the epidermis, dermis, or subcutaneous tissue. Furthermore, in some rare cases, systemic treatment may be needed if the skin disease and/or disorder is severe, recalcitrant, or fails to respond to topical drug treatment (7). For this reason, other BE approaches are usually required.

APPROACHES FOR BE ASSESSMENT OF TOPICAL DERMATOLOGICAL DRUG PRODUCTS

BE Studies with Clinical Endpoints

A BE study with a clinical endpoint is the approach that is most commonly required for BE assessment of topical drug products by international regulatory authorities and organizations. BE assessment is based on the documentation of equivalent safety and efficacy in patients. These studies are often designed as randomized, blinded, parallel studies using a placebo arm. The placebo arm is to confirm that there is a therapeutic response and detectable differences between the proposed generic and reference products. The selection of the appropriate clinical endpoint may depend on several factors such as disease, characteristic to measure, dosage regimen, and treatment population (8).

The assessment of the selected endpoint(s) can vary from binary (cure *versus* failure), categorical or continuous (severity based on a number scale), cause-specific *versus* all-cause, clinical *versus* surrogate, combined endpoint, dichotomous (success *versus* failure), and single event *versus* composite. Other factors that may also need to be considered is the unknown inter-subject variability within the reference product and difficulty in achieving consistency between the results of a BE study with a clinical endpoint. For instance, for antifungals and other anti-infectives, a false negative in the baseline may lead to exclusion of many patients. Whereas for acne products, there are multiple endpoints, so the selection of the endpoint to evaluate can have a direct impact on the outcome of the study (9). The above points may contribute in some manner to the high variability and low sensitivity in some cases to detection of formulation differences between drug products. In addition, BE studies with clinical endpoints

often require a large patient population (>500–600 patients), which are overall very costly and time consuming to perform (10).

BE Studies with Pharmacodynamic Endpoints

The most widely accepted surrogate approach by regulators for BE assessment of topical dermatological drug products is the McKenzie-Stoughton vasoconstrictor assay (VCA) (11,12). This pharmacodynamic (PD) approach is also known as the human skin blanching assay. The basis of the VCA approach is the measurement of the PD effect of the drug being assessed as a function of time. The desired PD effect is skin blanching or visible lightening. This is a result of vasoconstriction of the skin microvasculature. The PD endpoint is either visually assessed (scoring scale) or by instrumental detection, Chromameter readings. The study population is healthy human subjects. In 1995, the United States Food and Drug Administration (USFDA) issued a guidance for industry: *Guidance Topical Dermatologic Corticosteroids: In Vivo Bioequivalence* (issued 2 June 1995), which describes the VCA approach. Both a pilot study and pivotal BE study are recommended, and the data analysis is based on $E_{\max}$ model—population modeling (13,14).

The $E_{\max}$ model:

$$E = E_0 + \frac{E_{\max} \times D}{D + ED_{50}} \quad (1)$$

The $E_{\max}$ model for dermatological drug products data:

$$AUEC = \frac{AUEC_{\max} \times \text{Dose duration}}{\text{Dose duration} + ED_{50}} \quad (2)$$

Where,

AUEC	Pharmacodynamic effect metric (area under the effect curve)
$AUEC_{\max}$	Maximum fitted value of “AUEC”
D	Dose
E	Pharmacodynamic effect
E_0	Baseline effect
$E_{\max}$	Maximum fitted value “ E ”
ED_{50}	Dose duration necessary to achieve 50% of the $E_{\max}$ value

Duration of exposure of the skin to the products is used to control the dose. The initial pilot dose-duration response study is recommended in order to determine the appropriate dose duration for use in the subsequent pivotal BE study. In the pilot study, the initial estimation of the $E_{\max}$ is conducted using the reference product. The appropriate dose duration times ED_{50} , D_1 , and D_2 ($D_1 = ED_{50}/2$ and $D_2 = ED_{50} \times 2$) are selected based on the outcome of the pilot study. These dose-duration times are used to perform the pivotal BE study. The selection of the dose is critical in being able to distinguish between two products that may be quite different but appear bioequivalent.

For BE assessment, the pivotal BE study incorporates a replicate design and documentation of acceptable individual

subject dose-duration responses by comparing the two products. The PD response in both studies is most commonly assessed by a Chromameter. The AUEC from zero to D_1 (AUEC1) and to D_2 (AUEC2) are calculated for each subject, and the subjects who show more than 1.25 for the ratio (AUEC D_2 /AUEC D_1) are considered to be “detectors.” The data for these detector subjects are used for BE assessment. Based on this model, the proposed generic and reference drug products should meet the BE acceptance criteria in which the 90% CI is between 80.00% and 125.00% for the observed PD response.

Some of the major challenges with the VCA approach are in the pilot dose-duration-response study. In 2013, some of the challenges with this approach were presented at the Product Quality Research Institute (PQRI) workshop for topical drug products held in the USA (15). The challenges mainly dealt with the estimation of the ED_{50} value in the pilot dose-duration-response study. The estimation of the ED_{50} value can be affected by (1) the selection of the appropriate dose-duration times in the study; (2) low AUECs for doses and truncation of the dose-duration response; (3) impractical and shorter ED_{50} values; and (4) a possible bi-phasic dose-duration response. The potency of the drug product is a key factor for all of these challenges. For high potency drug products, the inclusion of early time points in the study may be necessary. Low potency drug products may produce a variable PD response that may include background noise and generate non-meaningful AUEC and ED_{50} values. Therefore, for low potency drug products, longer duration times along with occlusion of the testing sites may be necessary in order to reliably measure the ED_{50} value. The issue of a bi-phasic dose-duration-response profile may be evaluated by an alternative fitting method but this has to be further investigated (16). Overall, addressing these challenges continues to be an ongoing. However, despite these challenges the VCA approach is still widely accepted. As compared with BE studies with clinical endpoints, this approach is often less costly and time consuming. However, the VCA approach is only applicable to topical corticosteroids.

In Vivo Dermatopharmacokinetic Studies

The dermatopharmacokinetic (DPK) approach is based on the measurement of absorption of the drug into the stratum corneum as a function of time (17,18). This is due to the fact that much of the topically applied drug is absorbed into the skin and passes through the stratum corneum. This approach employs the tape stripping of successive layers of the stratum corneum after topical application over the specified time period. The study population is healthy human subjects. This approach is an alternative to costly BE studies with clinical endpoints. Also, unlike the VCA approach the DPK approach may be applicable to a variety of therapeutic classes of topical dermatological drug products. However, the acceptability of this approach is still hindered due to methodology and study design issues (19).

BE Studies with In Vitro Endpoints

BE studies with *in vitro* endpoints rely on *in vitro* characterization of the proposed generic and reference

products. This is directly based on the formulation performance of the drug products. There are multiple tests that can be employed with this approach. These tests include *in vitro* rheological tests which are used to assess the physiochemical properties (Q3) of the formulation. Tests to assess physicochemical properties may include pH, viscosity, specific gravity or density, surface tension, buffer capacity (if the product contains a buffer), droplet size or volume (if administered as drops), and droplet size distribution (if administered as a topical spray). Also, another *in vitro* approach is *in vitro* release testing (IVRT). This approach uses diffusion cells such as the Franz diffusion cell system.

The IVRT approach can be used to estimate the rate of drug release from the formulation. A difference in the drug release should reflect changes in the characteristic of the drug product formulation or the thermodynamic properties of the drug. In general, the IVRT approach can reflect the combined effect of several physical and chemical parameters, including solubility and particle size of the active pharmaceutical ingredient (API), along with the rheological properties of the dosage form. The Franz diffusion cell system has been used by the pharmaceutical industry for years during the developmental stage of topical drug products. It is also an accepted approach to support some post-approval changes for topical semi-solid dosage forms by the USFDA. The post-approval changes include (1) components or composition, (2) the manufacturing (process and equipment), (3) scale-up/scale-down of manufacture, and/or (4) the site of manufacture of a semi-solid formulation (20).

Waivers from BE Study Requirements

It is also possible to obtain a waiver from comparative BA/BE study requirements by most international regulatory authorities and organizations. Commonly waivers are only granted for topical solutions. The API and excipients in the formulation of the proposed generic product must be qualitatively (Q1) and quantitatively (Q2) the same as the reference product. Changes to the formulation can lead to denial of the waiver request or necessary submission of *in vivo* and/or *in vitro* BE studies. This is dependent upon each jurisdictional requirement.

GLOBAL MEETINGS AND CONFERENCES HELD TO DISCUSS REGULATORY REQUIREMENTS FOR BE ASSESSMENT OF TOPICAL DERMATOLOGICAL DRUG PRODUCTS

Over the last decade, several conferences and/or workshops have been held worldwide to discuss current acceptable BE approaches and the development of potentially new and promising approaches such as *in vivo* dermal microdialysis (DMD) and infrared spectroscopy (21–24). Some of the notable conferences include the 2005 and 2008 International Pharmaceutical Federation/Board of Pharmaceutical Sciences (FIP/BPS) international conference, Bio-International 2005 and 2008 at the Royal Pharmaceutical Society of Great Britain in London, UK (25,26). At the 2005 conference, BE issues related to generic locally acting topical drug products were discussed. The conference focused on the feasibility of alternative approaches such as PK and DPK for topical

dermatological drug products. At the 2008 conference, there was a discussion of improved efforts toward harmonization in regulating generic drug products. Again, there was a focus on complex BE issues such as topicals. During the conference, there was an overview of current BE approaches along with a discussion of alternative approaches such as DMD and DPK.

As stated previously, most recently in 2013, a 3-day workshop was held in the USA by PQRI (27). It was sponsored by the American Association of Pharmaceutical Scientists (AAPS), FIP, and United States Pharmacopeia (USP). During the workshop, there was extensive discussion of the current BE approaches, along with the progression of alternative approaches such as *in vivo* PK studies, DPK, DMD, and *in silico* methods for drug development and approval of generic and reference drug products. The USA and Canada also provided an overview of their current approval processes, along with current trends and strides in implementing new approaches for BE assessment (28,29).

In 2012, the International Generic Drug Regulators Pilot (IGDRP) Project was launched in order to support global harmonization. The goals of this pilot program are to promote collaboration and convergence in the generic drug regulatory programs and collectively address complex scientific issues (30). Currently, the participating jurisdictions include Australia, Brazil, Canada, China, Chinese Taipei, the European Directorate for the Quality of Medicines and Healthcare (EDQM), the European Medicines Association (EMA), Japan, Mexico, New Zealand, Russia, Singapore (a member of the Association of Southeast Asian Nations, ASEAN), South Africa, South Korea, Switzerland, the USA, and the World Health Organization (WHO). As previously reported in Davit *et al.* (31), the definitions of generic and reference products are provided for most of the jurisdictions and organizations. The definition of a generic drug product is similar among all jurisdictions and organizations (31–33).

METHODS

The objective of this review is to summarize and compare the individual BE approaches for topical dermatological drug products across international jurisdictions and organizations. As outlined in Table I, the current BE approaches included in this review are for the following 15 international jurisdictions and organizations: Australia, Brazil, Canada, China, Chinese Taipei, the EMA, Japan, Mexico, New Zealand, Singapore, South Africa, South Korea, Switzerland, the USA, and the WHO. The EDQM currently does not have any guidelines for topical drug products. Therefore, this organization will not be included in the evaluation. We compared the similarities and differences in BE approaches required by each regulatory agency corresponding to each jurisdiction. The following six BE approaches were compared:

- BE studies with clinical endpoints
- BE studies with PD endpoints
- BE studies with PK endpoints
- *In vivo* DPK studies
- BE studies with *in vitro* endpoints
- Waivers from BE study requirements

Table I also provides a listing of the published guidance's for industry, individual agency policies, and regulations for each regulatory agency and organization. All of these published documents along with other literature were the sources of the information provided in this review (32–58). It should be noted that Australia and Switzerland have both adopted the EMA guidance documents for BE assessment (34–36). Also, Singapore currently follows the ASEAN guidance documents. In March 2013, China and Korea each changed its regulatory agency name. China changed its regulatory agency name from State Food and Drug Administration (SFDA) to China Food and Drug Administration (CFDA). South Korea changed its agency name from Korea Food and Drug Administration (KFDA) to Ministry of Food and Drug Safety (MFDS). For the remainder of this document, a generic drug product will be referred to as a test product.

RESULTS

Specific Guidelines for BE Assessment of Topical Dermatological Drug Products

As outlined in Table I, only Canada, the EMA, Japan, and the USA have guidance documents specific for topical drug products. In each of the guidance documents, a detailed description of the current BE approaches based on site of action, therapeutic drug class, and/or complexity of the dosage form, i.e., solution *versus* semi-solids are provided. For Japan, the BE approaches required for most topical drug products are outlined in one detailed guidance document. The EMA and the USA currently have a guidance document specific for topical corticosteroids. In addition, since 2007 the USA has been publishing product-specific BE recommendations for the public (37). Currently, there are over 100 drug specific guidance documents posted for topical drug products. In general, the individual guidance outlines the study design and conduct of the BE study, along with the BE acceptance criteria. For all other jurisdictions and organizations, the identification of BE approaches for topical drug products are incorporated into each of their comparative BA/BE guidance documents. The information provided in the current guidance documents for Brazil, Mexico, Singapore, and South Korea is very limited for these particular drug products.

BE Studies with Clinical Endpoints

For almost all jurisdictions and organizations, BE studies with clinical endpoints are required for approval of most topical drug products unless otherwise specified in Table II. Both safety and efficacy must be demonstrated in order to obtain approval. In all cases, the design of the clinical study is pivotal. Also, an appropriate clinical endpoint and statistical method should be selected and employed for evaluation of the data. For almost all jurisdictions and organizations, additional studies may be required due to safety concerns. The EMA guideline specifically outlines the conditions for potentially requiring an additional study. One of the conditions is if more of the API of the test product is systemically absorbed than the reference product. Also, additional clinical studies may be necessary due to possible hypothalamic-

Table I. Listing of BE Guidance Documents, Policies, and Regulations for International Regulatory Authorities and Organizations Representing Various Jurisdictions

	Jurisdiction/organization	Regulatory agency
BE guidelines/ policies/regulations	Australia	Therapeutics Goods Administration (TGA)
	Follows the EMA guidelines unless otherwise specified (34,38)	
	Brazil	National Agency of Sanitary Monitoring (ANVISA)
	Guide for relative bioavailability/Bioequivalence tests of drug products—May 2003 (39)	
	Canada	Health Canada (HC)
	Policy, submissions for generic topical drugs—September 1990 (41)	
	Notice, guidance for industry: pharmaceutical quality of aqueous solutions—February 2005 (42)	
	Guideline, conduct, and analysis of comparative bioavailability studies—May 2012 (43)	
	China	China Food and Drug Administration (CFDA)
	Bioavailability and bioequivalence studies for chemical drug products—March 2005 (45)	
	Chinese Taipei (Taiwan)	Taiwan Food and Drug Administration (TFDA)
	Guideline for bioavailability/bioequivalence studies—April 2009 (46)	
	European Union (EU)	European Medicines Agency (EMA)
	Clinical investigation of corticosteroids intended for use on the skin—February 1987 (48)	
	Clinical requirements for locally applied, locally acting products, containing known constituents—November 1995 (49)	
	Questions and answers on guideline title: clinical investigation of corticosteroids intended for use on the skin—November 2006 (50)	
	Guideline on investigation of bioequivalence—January 2010 (35)	
	Japan	Ministry of Health, Labour and Welfare (MHLW)
		Pharmaceutical and Medical Devices Agency (PMDA)
	Guideline for bioequivalence studies of generic products for topical use—July 2003 (51)	
	Guideline for bioequivalence studies for generic products—February 2012 (52)	
	Mexico	The Federal Commission for the Protection Against Sanitary Risk (COFEPRIS)
	Guidelines for the implementation of the standard Nom-177-SSA1-1998 establishing test and procedures for demonstrating that a product is interchangeable—October 2012 (36)	
	Guidelines for submission of research protocols to demonstrate the drug interchangeability—November 2012 (36)	
	New Zealand	Medsafe
	New Zealand regulatory guidelines for medicines—November 2011 (32)	
	Singapore	Health Sciences Authority (HSA)
	Association of Southeast Asian Nations (ASEAN) guidelines for the conduct of bioavailability and bioequivalence studies—July 2004 (53)	
	Guidance on medicinal product registration in singapore—product interchangeability and biowaiver request for chemical generic drug applications, Appendix 15—February 2007 (54)	
	South Africa	Medicines Control Council
	Biostudies—June 2011 (33)	
	South Korea	Ministry of Food and Drug Safety (MFDS)
	Guidance document for bioequivalence study—December 2008 (36)	
	Switzerland	Swissmedic
	Follows the EMA guidelines unless otherwise specified (36)	
	United Nations	World Health Organization (WHO)
	Multisource (generic) pharmaceutical products: guideline on registration requirements to establish interchangeability (draft revision)—October 2005 (55)	
	USA	United States Food and Drug Administration (USFDA)
	Topical dermatologic corticosteroids: <i>in vivo</i> bioequivalence—June 1995 (13)	
	Bioequivalence recommendations for specific products—June 2010 (37)	
	Code of Federal Regulations (CFR): 21 CFR 314.94 (a) (9) (v), 21 CFR 320.21, 21 CFR 320.22 (b) (3), 21 CFR 320.22 (c), and 21 CFR 320.24 (b) (6) (57–58)	

BE bioequivalence, EMA European Medicines Association

pituitary gland (HPA axis) suppression by some topical corticosteroids. In the latter case, the same requirement may be made by the USA.

The selection of the clinical endpoint is critical for all jurisdictions and organizations. In the USA, the endpoints used in the study are recommended based on the product-specific indication. If there are multiple indications, then the indication that is most sensitive to difference in local drug

delivery of the drug is usually preferred. This is due to the fact that in some instances the selected endpoint may not be sensitive to formulation differences between the two products. Also, depending on the endpoint will dictate the criterion used to establish BE. The BE acceptance criteria is based on the nature of the endpoint.

In the USA for a continuous endpoint, the 90% confidence interval (CI) of the test-to-reference ratio of means must be

Table II. Similarities and Differences in the BE Requirements and Design of BE Studies with Clinical Endpoints for Topical Dermatological Drug Products

Criteria for selection and design of BE studies with clinical endpoints for topical dermatological drug products	
Similarities	<ul style="list-style-type: none"> • BE studies with clinical endpoints are required for most topical drug products by almost all jurisdictions and organizations • Additional BE studies with clinical endpoints may be required due to safety concerns for almost all jurisdictions and organizations
Differences	<ul style="list-style-type: none"> • Australia, the EMA, and Switzerland: for safety issues, in general safety and local tolerance may be guaranteed by knowledge of the API and its excipients. If more of the API from the generic reaches the site of action and/or systemic circulation is higher than the reference product then an appropriate toxicological, pharmacological, and human data will be necessary to show the compound is indeed inactive and has no interaction with the API. In addition for topical corticosteroids, hypothalamic-pituitary-adrenal (HPA) axis suppression may occur. To address this safety concern, typically a clinical study with a parallel study design that monitors the plasma cortisol levels before and after prolonged applications (e.g., 4 weeks) of the test and reference product is also necessary As it pertains to efficacy, the study design is pivotal. In most cases, a three-arm study is conducted comparing the placebo and the test and reference drug products. The BE acceptance criteria will be based on the drug being studied and parameters used for appropriate evaluation of “equivalence.” Therefore, the 90% confidence interval (CI) of 80.00–125.00% (20% variation) may not always be acceptable • Brazil, China, Chinese Taipei, Mexico, and South Korea: the referenced guidance documents do not specify or mention the criteria for BE studies with clinical endpoints specific to topical dermatological drug products Note: In China, in general BE studies with clinical endpoints can be required to demonstrate BE when PK or PD approaches are not feasible • Canada, New Zealand, Singapore, and South Africa: the study design of a BE study with a clinical endpoint is not outlined in detail in the referenced guidance documents or policies for locally acting topical dermatological drug products • Japan: the BE acceptance criteria is based on the clinical efficacy of the test and reference products • USA: a BE study with a clinical endpoint will use the product-specific indications recommended by the USFDA. If the reference product is labeled for multiple indications, the indication that is most sensitive to difference in local delivery of the drug is usually preferred. The BE acceptance criteria for BE studies with a clinical endpoint is based on the type of endpoint • WHO: a general guideline for the design of a comparative clinical trial is outlined in the referenced guideline. Where appropriate, a placebo arm should be include in the design of the study. In some cases, it is relevant to include safety-endpoints in the final comparative assessments. The size of the acceptance range has to be defined by a case-by-case basis taken into consideration the specific clinical conditions. At present, the statistical method is based on the 90% CI approach. In some instances, one-sided CI may be appropriate. The CIs can be derived from either parametric or non-parametric methods

BE bioequivalence, EMA European Medicines Association, API active pharmaceutical ingredient, WHO World Health Organization, PD pharmacodynamic, USFDA United States Food and Drug Administration, CI confidence interval, PK pharmacokinetic

within 0.80–1.25. The study is designed as a randomized, double-blind, parallel, placebo-controlled study. An example for this is Acyclovir Ointment when clinical trials are necessary. Immuno-compromised males and non-pregnant females with recurrent herpes simplex are enrolled in the study. The recommended primary endpoint is time to complete healing of lesions. This is defined as the loss of crust and re-epithelialization with or without erythema, as assessed by the investigator, based on a clinical observation (59).

For a dichotomous endpoint, the difference between the test and reference products must be within -0.20 and $+0.20$. An example of this is Tacrolimus Ointment. The study is designed as a randomized, double-blind, parallel, placebo-controlled study. Non-immunocompromised male and female adults with clinical diagnosis of moderate to severe atopic dermatitis are enrolled in the BE study with clinical endpoints. The primary endpoint is the proportion of subjects with treatment success (a grade of clear or almost clear; a score of 0 or 1 within the treatment area) based on the Investigators Global Assessment of Disease Severity (37).

BE Studies with PD Endpoints

The most widely accepted alternative approach to BE studies with clinical endpoints is the VCA approach. However, as stated previously this approach is only applicable to

topical corticosteroids. Australia, Canada, Chinese Taipei, the EMA, New Zealand, and Switzerland currently follow the USFDA guideline for topical corticosteroids (Table III). In Japan, the recommended design and conduct of the VCA approach is similar to the current VCA approach recommended in the USA. Brazil, China, Korea, Mexico, Singapore, South Africa, and the WHO may require BE studies with PD endpoints. However, the referenced guidance documents for these jurisdictions and organization do not provide a detailed outline of the design and/or conduct of a PD study for topical dermatological drug products.

For some jurisdictions and organizations, the dosage form and/or site of application may have an impact on the acceptability of BE studies with PD endpoints. For instance in Brazil, PD studies may be required for topical creams but may not acceptable for other topical dosage forms. Also, in South Africa the VCA approach is required for topical corticosteroids that are applied to the skin and scalp. In contrast, the USA currently only requires the VCA approach for topical corticosteroids that are applied to the skin and not scalp products (60). This is because of the differences in scalp and non-scalp skin. This is attributed to the fact that an effective topical drug product formulation must take into consideration the *in vivo* environment from which the API is delivered to the site of action (3,6).

Table III. Similarities and Differences in the BE Requirements and Design of BE Studies with PD Endpoints for Topical Dermatological Drug Products

Criteria for selection and design of BE studies with PD endpoints for topical dermatological drug products	
Similarities	Australia, Canada, Chinese Taipei, the EMA, New Zealand, and Switzerland: currently, follow the USFDA guidance to industry for topical dermatologic corticosteroids
Differences	<ul style="list-style-type: none"> • Australia, the EMA, and Switzerland: in addition to VCA studies, local tolerance studies are usually necessary. The preferred design is a double-blind vehicle controlled repeated application. Both the corticosteroid and its vehicle are applied on healthy skin under occlusion (to increase possible irritation/insult) 3 times a week for 2 to 3 weeks (study duration will depend on the recommended duration of treatment). Irritation is graded on a 5-point scale at the end of the trial. If there is reason to believe that tolerability on diseased skin may be altered even by the minor changes of the test product, e.g., by changing physical consistency of a cream or ointment, additional tolerability studies in patients may be necessary • Brazil: a BE study with a PD endpoint may be allowed for topical drug products such as creams. The applicability of this type of study depends on the dosage form. No further details are provided in the referenced guidance document • China: in general, a BE study with a PD endpoint may also be required when PK studies are not feasible for certain drug products. However, no further detail is provided in the referenced guidance document • Japan: both a pilot study and pivotal BE study are recommended. The pilot study is conducted to determine the dose-duration times (T_{50}, half-maximal effect, $T_1 (T_{50}/n)$ and $T_2 (T_{50} \times n)$), where n is either 2 or 3. The pivotal BE study is conducted in order to assess BE between the test and reference drug products by calculation of the AUEC values for each subject. The AUEC from zero to T_1 (AUEC1) and to T_2 (AUEC2) are calculated for each subject, and the subject who shows more than 1.25 for the ratio (AUEC2/AUEC1) is considered to be a responder. According to the guidance document, it is desirable to employ responder subjects only for the skin blanching test. However, it is acceptable to include additional subjects in the study in order to satisfy the statistical assessment after removal of non-responders. The assessment of the pharmacological response can be conducted through visual assessment (scale 0–3 or 4 or higher) by human observers or Chromameter. When the PD response is visually assessed, the 90% CI is based on the difference in the area under the effect curve (AUEC) between the test and reference drug products calculated by a non-parametric method or parametric method after the logarithmic transformation of the AUEC values. Whereas, when the PD response is assessed via a Chromameter, the AUEC values should not be log-transformed since they are usually negative values. The 90% CI of the difference in mean AUEC values between the test and reference drug products is calculated using raw data and non-parametric methods. The acceptable BE criteria are generally 0.8–1.25 for the test/reference drug product ratio of average values, when the parameters are log-transformed. The acceptable BE criteria is generally –0.2 to +0.2 for the relative difference <i>in vivo</i> parameters between test and reference drug products, when the raw data are used • Mexico and South Korea: the referenced guidance documents do not specify or mention the criteria for BE studies with PD endpoints for topical drug products • Singapore: a BE study with a PD endpoint may also be required for topical drug products. However, no further detail is provided in the referenced guidance document • South Africa: the VCA approach is applicable for topical corticosteroids being applied to the skin and scalp. Visual and/or Chromameter data will be necessary. However, no further detail is provided in the referenced guidance document • USA: as of 2009, the VCA approach is only applicable to topical corticosteroids that are applied to non-scalp skin. If a topical drug product is applied to the scalp then either a waiver may be granted or clinical endpoint study will be necessary. This latter statement is based on the formulation of the drug product • WHO: a general outline for the design of a BE study with PD endpoints is provided in the referenced guidance document. The description of the study design is general and not specific to a drug class. In general, the PD study should be designed to demonstrate that the PD response which is relevant to the safety and/or efficacy. Neither the test or reference product should produce maximal response in the course of the study. In addition, investigation of dose–response relationships may be necessary as part of the study design. The PD response should be measured quantitatively, preferably under double-blind conditions, and also be recordable by an instrument that produces and records the results of repeated measurements to provide a record of the PD event. Where such measurement is not possible then visual assessment can be used. If the data are limited by qualitative measurements then appropriate special statistical analysis will be necessary. All participants in the study should be screened prior to the study to exclude non-responders. In addition, the criteria by which responders are distinguished from non-responders should be stated in the protocol. Also, the method should be validated

BE bioequivalence, EMA European Medicines Association, VCA vasoconstrictor assay, WHO World Health Organization, PD pharmacodynamic, USFDA United States Food and Drug Administration, CI confidence interval, PK pharmacokinetic

BE Studies with PK Endpoints

As stated previously, PK studies are not commonly required for topical dermatological drug products. Two possible reasons these studies may be required is due to safety concerns based on unintended systemic exposure or the drug product is intended for systemic absorption. In both cases, the drug concentration in the biological matrix is measured. As outlined in Table IV, Australia, Canada, the EMA, Japan, Singapore, South Africa, Switzerland, the USA, and the WHO may require the submission of these

particular studies due systemic exposure of the drug product. Japan and the USA also deem these studies necessary for BE assessment in certain cases and for certain drug products. In Japan, PK studies are necessary when the active site of the drug is the stratum corneum and/or below and if the clinical efficacy or drug concentration in the active site correlates with the PK parameters. The USA currently requires a PK study for Lidocaine Patch and Diclofenac Gel (37). Both of these drug products are topically applied and are systemically absorbed. The BE acceptance criteria in both cases is 80.00–125.00%.

Table IV. Similarities and Differences in the BE Requirements and Design of BE Studies with PK Endpoints for Topical Dermatological Drug Products

Criteria for selection and design of BE studies with PK endpoints for topical dermatological drug products	
Similarities	<ul style="list-style-type: none"> • Australia, Canada, the EMA, Japan, Singapore, South Africa, Switzerland, the USA, and the WHO may require BE studies with PK endpoints • In most cases these particular studies are required due to the following reasons: (1) safety concerns based on systemic exposure and/or (2) drug product is intended for systemic absorption
Differences	<ul style="list-style-type: none"> • Australia, the EMA, and Switzerland: whenever systemic exposure occurs due to locally applied topical drug products then the systemic exposure should be measured. It should be demonstrated that there is no difference in the systemic exposure between the test and reference products, i.e., the 90% CI should not exceed the upper BE acceptance criteria of 125.00% (80.00–125.00%) for all the specified PK parameters • Brazil, China, Chinese Taipei, Mexico, New Zealand, and South Korea: the referenced documents do not specify or mention the criteria for BE studies with PK endpoints for topical dermatological drug products • Japan: a PK study is normally employed when the active site of the drug is the stratum corneum and/or below and if the clinical efficacy or drug concentration at the active site correlates with the PK parameters. The duration of application of the test and reference drug products should follow the dosage regimen or is equal to or longer than the time to reach steady state. The pivotal study is conducted according to the guidance document. The BE acceptance criteria is based on the PK parameters of area under the curve (AUC) and steady-state drug concentration (C_{ss}). The mean values of these parameters should be within (0.8–1.25) • USA: there are only a few instances in which a PK study is required for topical drug products. This is either due to safety reasons or BE assessment. The 90% CIs for the specified PK parameters (AUC_T, AUC_I, C_{max}) should meet the BE acceptance criteria of 80.00–125.00%

BE bioequivalence, EMA European Medicines Association, WHO World Health Organization, CI confidence interval, PK pharmacokinetic, C_{max} maximum concentration

***In Vivo* DPK Studies**

Currently, Japan and South Africa are on the only jurisdictions that may accept *in vivo* DPK studies (Table V).

The WHO also mentions DPK studies in its guideline. However, no specific details are provided in the guidelines of South Africa or the WHO. For Japan, the stipulation for acceptance of this approach is the drug must not damage the

Table V. Similarities and Differences in the BE Requirements and Design of *In Vivo* DPK Studies for Topical Dermatological Drug Products

Criteria for selection and design of <i>in vivo</i> DPK studies for topical dermatological drug products	
Similarities	Japan and South Africa are currently the only jurisdictions that may accept DPK studies
Differences	<ul style="list-style-type: none"> • Australia, Brazil, Canada, China, Chinese Taipei, the EMA, Mexico, New Zealand, Singapore, South Korea, and Switzerland: the referenced guidelines do not specify or mention the criteria for <i>in vivo</i> DPK studies • Japan: these studies are only applicable to topical drug products whose site of action is the stratum corneum itself or deeper. Both a pilot study and pivotal BE study are recommended. The pilot study is performed in order to (1) the dose applied, the time and skin area for the product application and skin stripping, (2) establish and validate the extraction of drug from the adhesive tape and analytical method, (3) the time to reach steady state, and (4) the number of sites to be used in the pivotal study. In this study, the drug uptake into the stratum corneum can be measured using the transepidermal water loss (TEWL). In the pivotal study, the skin sites are allocated randomly for treatment with the test and reference products. The sites should be marked. The drugs are applied for the allotted time. Removal of the drug from the skin occurs at the designated time and the residual ointment or cream remaining on the skin is removed. Then, the surface layers of the skin are peeled off with two adhesive tapes which are discarded since the drug contained in the layers are generally not considered to be absorbed. The strip of the stratum corneum sequentially with adhesive tape which differs depending on whether the drug concentration in the stratum corneum is estimated or not based on the following equation: $TEWL = \frac{K_w D_w \Delta C}{L} \quad 3$ <p>Where K_w is the partition coefficient of water between stratum corneum and epidermal cell, D_w is the diffusion constant of water through the stratum corneum; ΔC is the difference in concentration of water between the surface and deepest point of the stratum corneum; and L is the thickness of the stratum corneum</p> <p>The measurement is of the amount of the drug received in each container. When the equation is not used, determine the drug amount recommended from the stratum corneum to the average drug concentration, which is determined by dividing the total amount of drug received by the total weight of the stratum corneum. When the same product is applied to multiple sites per each subject, the average drug uptake should be determined and used for BE assessment. <i>In vivo</i> parameters at a steady state should be logarithmically transformed, and the 90% CI interval of the test/reference ratio of the average values is calculated by a non-parametric method (0.8–1.25)</p> • South Africa and the WHO: this approach is mentioned in the referenced guidance documents. However, no details are provided as to how this particular study should be performed • USA: the USFDA currently does not accept this approach

DPK dermatopharmacokinetic, BE bioequivalence, EMA European Medicines Association, WHO World Health Organization, USFDA United States Food and Drug Administration, CI confidence interval

Table VI. Similarities and Differences in the BE Requirements and Design of BE Studies with *In Vitro* Endpoints for Topical Dermatological Drug Products

Criteria for selection and design of BE studies with <i>in vitro</i> endpoints for topical dermatological drug products	
Similarities	<ul style="list-style-type: none"> • Brazil, the EMA, South Africa and the USA may require <i>in vitro</i> studies alone for approval of topical dermatological drug products • Most other jurisdictions and organizations may require <i>in vitro</i> studies as supportive evidence for granting of waivers from BE study requirements or other BE studies submitted for approval
Differences	<ul style="list-style-type: none"> • Australia, the EMA, and Switzerland: <i>in vitro</i> studies may be considered provided that all studies are adequately validated • Brazil: only <i>in vitro</i> studies are necessary for topical dermatological drug products which are non-corticosteroids and dosage forms are semi-solids, such as creams, ointments, lotions, etc. The design and/or type of studies are not outlined in the referenced guidance document • Canada: <i>in vitro</i> tests are required in support of waiver requests. The physiochemical properties tests that are generally included in comparative studies are description, pH, viscosity, specific gravity or density, surface tension, droplet size or volume (if administered as drops), droplet size distribution (if administered as a spray), and delivered dose uniformity (if packaged with a device for delivery) • China, Chinese Taipei, Mexico, New Zealand, Singapore, and South Korea: the referenced guidance documents do not specify or mention the criteria for <i>in vitro</i> studies for topical drug products • Japan: <i>in vitro</i> release tests and <i>in vitro</i> efficacy tests may be accepted as supportive evidence, along with the BE tests. The test should be performed using 6 units or more for three lots of the reference product at 32°C, by appropriate methods such as USP paddle-over disk method or diffusion cell which can estimate their drug release. Aqueous test fluids, aqueous alcohol solutions, or other alternative solutions may be used as a test fluid. When release tests are carried out using membranes to separate test fluids and dosage forms, the permeation of the membrane should not be the rate-determining step for the drug release. Among the three lots, the one which shows intermediate release should be selected as the reference product. As the test product of generic drugs, an industrial scale-lot should be used. However, a lot of 1/10 or larger of industrial scale can also be used as the test product which should be the same as the production lots in manufacturing method, quality, and bioavailability. The drug content or potency of the reference product should be close to the label claim, and the difference in drug content or potency between test and reference products should be less than 5% <i>In vitro</i> efficacy studies may be applicable for topical drug products whose site of action is the stratum corneum itself or deeper. This test uses <i>in vitro</i> activity as the index for BE assessment. These studies may be applicable for topical drug products whose active site is the surface of the skin and the drug from the product does not need to be absorbed through the stratum corneum. Examples of this are bactericides, disinfectants, and antiseptics. The <i>in vitro</i> efficacy test does not include a drug release test for topical drug products. The acceptance criteria for BE in this study should be established for each drug by considering the characteristics of the efficacy • South Africa and the WHO: this approach is mentioned in the referenced guidance documents. However, no details are provided as to the criteria for selection of these studies and/or design of these <i>in vitro</i> studies • USA: as of 2012, the USFDA require BE studies with <i>in vitro</i> endpoints. However, the current case is only Acyclovir Ointment. In addition to submission of acceptable <i>in vitro</i> tests, the formulation of the test product must be Q1/Q2/Q3 the same as the reference product

EMA European Medicines Association, WHO World Health Organization, USFDA United States Food and Drug Administration, BE bioequivalence

1st layer of the stratum corneum. In the 1990s, the USA previously considered this approach for BE assessment of topical drug products (61). In 1992, the USFDA issued the interim guidance, *Topical Corticosteroids: In Vivo Bioequivalence and In Vitro Release Approaches*, which included the skin stripping technique, along with PK and IVRT. However, it was later concluded that there was insufficient data to recommend this approach. Therefore, it was removed from the current guidance issued in 1995 for topical corticosteroids.

Three years later in 1998, the USFDA issued the draft guidance: *Topical Dermatological Drug Product NDAs and ANDAs-In Vivo Bioavailability, Bioequivalence, In Vitro Release, and Associated Studies* (62). In this guidance, the DPK approach was once again recommended as an approach for BE assessment of topical dermatological drug products. The approach was deemed comparable to the PK approach used in systemically available drug products by being able to determine drug concentration as a function of time (5). The guidance also discussed the stratum corneum and follicular penetration. In the draft guidance, a pilot study and a pivotal

BE study were proposed. It also included the recommendations for performance and validation of the technique.

The metrics of the pivotal BE study were time to reach the maximum concentration (T_{max}), the maximum concentration (C_{max}), and the area under the concentration t time curve (AUC). The BE acceptance criteria was 80.00–125.00 and 70.00–143.00% for AUC and C_{max} , respectively. However, the guidance was withdrawn in 2002 after years of scientific research, following public comments and USFDA Advisory Committee discussions in 1998, 2000, and 2001. The major scientific concerns were the doubt of adequacy to assess BE of topical dermatological drug products since they are used to treat a variety of diseases in different parts of the skin not just the stratum corneum and the reproducibility of the method across laboratories. There were collaborative research studies conducted prior to and during the issuance of this guidance.

Although, the DPK approach is currently not accepted by the USFDA for BE assessment of topical drug products it is still being evaluated as a possible approach that will be potentially accepted in the future. The USFDA has embarked on recent collaborative projects. Moreover, as a follow-up to

these initiatives, the USFDA has continued to reiterate the importance of addressing these scientific challenges by incorporating this into the agreed upon regulatory initiatives in 2013 as a part of Generic Drug User Fee Amendments implementation (63).

Another *in vivo* approach that may be accepted by Japan is measurement of unabsorbed drug on the surface of the stratum corneum. The study is based on the estimation of the amount of drug absorbed into the skin from the amount remaining in the product after application. However, this test is limited since the uptake of many topical drugs is often very low, making it difficult to obtain a precise estimate of absorption. Yet, based on the NIHS guideline, it has been determined that this may be useful if precise estimation is possible. Both a pilot study and pivotal BE study are recommended. The amount of drug distributed into the skin following application of the product is used to measure BE. The data should be logarithmically transformed, and the 90%

CI of the test and reference ratio of the average value by a parametric method (0.8–1.25).

BE Studies with *In Vitro* Endpoints

In general for all jurisdictions *in vitro* tests may be required in order to support other *in vivo* studies and/or waiver requests from BE study requirements. Table VI outlines the similarities and differences in the criteria for selection of these particular studies. Currently, only Australia, Brazil, the EMA, South Africa, Switzerland, and the USA may accept these types of studies alone for approval of a topical drug product. According to the referenced guideline for Brazil, *in vitro* tests are necessary for non-corticosteroids and dosage forms which are semi-solids. However, no specific details as to the type of *in vitro* studies are provided. This is the same in South Africa. As of 2012, the USA may require *in vitro* endpoint studies for topical drug products with a

Table VII. Similarities and Differences in the Criteria for Granting of a Waiver from BE Study Requirements for Topical Dermatological Drug Products

Criteria for granting a waiver from BE study requirements for topical dermatological drug products	
Similarities	<ul style="list-style-type: none"> • Almost all of the jurisdictions may grant a waiver from <i>in vivo</i> BE study requirements for an aqueous topical solution • In general, the formulation of the test product should be Q1 and Q2 the “same” as the reference product for both API and excipients • If there is a difference in the excipients then each jurisdiction and organization additional BE documentation by performance of additional <i>in vivo</i> and/or <i>in vitro</i> studies may be required
Differences	<ul style="list-style-type: none"> • Australia, the EMA, and Switzerland: a waiver may be granted for both aqueous and oily topical solutions. Minor differences in the excipient composition may be acceptable if the relevant pharmaceutical properties between the two products are identical or essentially similar. All differences should satisfactorily be justified in relation to therapeutic equivalence • Brazil, China, Japan, and Mexico: the referenced guidelines do not specify or mention the criteria for granting waivers for topical drug products • Canada: The excipients in the test product should be Q1 and Q2 “essentially the same” as the formulation of the reference product. “Essentially the same” means the amount or concentration of each excipient in the generic product is within $\pm 10\%$ of the amount in the reference product. The differences in formulation should be scientifically justified and the potential impact on safety and/or efficacy of the drug product should be discussed. For excipients that modify absorption (enhance or inhibit) their concentrations should be essentially the same. In addition, comparative physiochemical property data should be provided to support a waiver request • Chinese Taipei: a waiver may be granted for topical solutions that are for external dermal uses, excluding drugs absorbed through hypodermic or intradermal routes • New Zealand: a waiver may be granted for a topical or locally acting solutions that have the same formulation • Singapore: a waiver may be granted for a test product that is intended to act without systemic absorption when applied locally • South Africa: a waiver may be granted for topical solutions (such as bacteriostatic, bactericidal, antiseptic, and/or antifungal claims). The inclusion of <i>in vitro</i> tests will also be necessary to support the waiver request from <i>in vivo</i> BE study requirements • USA: a waiver may be granted for aqueous and oily topical solutions. In accordance with 21 CFR 320.22 (b) (3), a waiver may be granted for a solution that is applied to the skin. The API should be in the same concentration as the reference product and no excipient or change in formulation should affect the local availability. In general, Q1 and Q2 differences should not be more than $\pm 5\%$ <p>In addition, in accordance with 21 CFR 314.94 (a) (9) (v), changes in excipients may be accepted provided the differences are identified and characterized. Also, information should be provided demonstrating that the differences do not affect safety and/or efficacy of the product</p> <p>Caveats: based on 21 CFR 320.22 (c), waivers are also granted for topical drug products that are considered as drug efficacy study implementation (DESI) drugs. These are drug products approved in the USA between 1938 and 1962. This applies to numerous topical drug products in a variety of topical dosage forms</p> <p>Topical corticosteroid solutions intended for application to scalp skin must be exactly Q1 and Q2 to the reference product. If not, then a clinical endpoint study is necessary</p> <ul style="list-style-type: none"> • WHO: a waiver may be granted for topical aqueous solutions, whose formulation contains the same API(s) in the same molar concentration and are essentially the same the same excipients in comparable concentrations. If there are any differences in the excipients, then data should be provided to demonstrate the differences will not affect the safety and/or efficacy of the product. In certain cases, the applicant may need to perform studies to demonstrate that the differences in excipients or devices do not affect product performance

simple formulation on the basis of 21 CFR 320.24 (b) (6). Currently, the only such case is Acyclovir Ointment (59). The test product must show that it is Q1/Q2/Q3 the same as the reference formulation. The EMA may consider *in vitro* or even animal studies provided that all studies used are adequately validated. In Japan, *in vitro* release tests may be accepted as an index for BE assessment. These are additional supportive studies to the required tests. Two examples are *in vitro* efficacy tests and *in vitro* release tests (51).

Waiver from BE Study Requirements

Granting a waiver from BE study requirements is most commonly based on the formulation and dosage form of the drug product. As outlined in Table VII, mostly all jurisdictions may grant a waiver for a topical solution providing the formulations of the test and reference products are the same. The API and excipients must be Q1 and Q2 the same as the reference product. Some jurisdictions and organizations do allow for slight differences in excipients. However, these differences should not modify absorption of the API or impact the safety and/or efficacy of the drug product. Canada, the EMA, the USA, and the WHO outlined in greater detailed the conditions in which differences in excipients may be acceptable. The differences still have to be in a certain range to be considered the “same” as the reference product. For instance, Canada and USA make a clear specification as to what “sameness” means. In Canada, the quantitative difference in excipients should be within $\pm 10\%$, whereas in the USA the difference should be no greater than $\pm 5\%$. It is necessary that for all cases if there are any differences in the formulations, especially if it can potentially impact absorption or release of the drug (penetration enhancers/inhibitors) then a justification and potential submission of additional

supportive data such as *in vivo* studies and/or *in vitro* studies, along with physicochemical property data are provided.

CONCLUSION

In this review, we identified the similarities and differences in the current BE requirements for topical dermatological drug products. Table VIII provides an overall summary of all of the approaches that are utilized by each of the international jurisdictions and organizations. From this table, it is observed that there is consistency in the BE approaches that may be recommended in order to meet the regulatory requirements for approval of these particular drug products. The three BE approaches that are currently consistently required are (1) BE studies with clinical endpoints for most topical drug products; (2) *in vivo* PD studies, in particular; the VCA approach for topical corticosteroids; and (3) waivers from BE study requirements for topical solutions. Most of the international regulatory authorities and organizations deem PK studies necessary in cases of safety concerns due to systemic absorption.

In addition, some may also request *in vitro* studies as supportive evidence for other *in vivo* studies and/or waiver requests. Currently, Japan, South Africa, the USA, and the WHO are leading the way in the acceptance of other approaches such as *in vivo* DPK studies, PK studies for BE assessment, and/or *in vitro* studies alone for approval of topical dermatological drug products. The information provided in this review can be useful in addressing the current regulatory and scientific issues that continue to arise for these particular drug products from a global regulatory perspective. As we continue to move forward, there is potential for alignment and consistency in regulatory approaches to establish BE

Table VIII. Summarization of BE Approaches for Locally Acting Topical Dermatological Drug Products Based on International Jurisdictions and Organizations

Summarization of BE approaches based on the data presented in Tables II, III, IV, V, VI, and VII

International jurisdiction/ organization	Comparative clinical trials	BE studies with PD endpoints	BE studies with PK endpoints ^b	<i>In vivo</i> DPK studies	<i>In vitro</i> studies ^c	Biowaivers (solutions)
Australia	●	●	●		●	●
Brazil ^a		●			●	
Canada	●	●	●			●
China	●	●				
Chinese Taipei ^a		●				●
EMA	●	●	●		●	●
Japan	●	●	●	●	●	
Mexico ^a						
New Zealand	●	●				●
Singapore/ASEAN	●	●	●			●
South Africa	●	●	●	●	●	●
South Korea ^a						●
Switzerland	●	●	●	●	●	●
United Nations/WHO	●	●	●	●	●	●
USA	●	●	●		●	●

BE bioequivalence, PK pharmacokinetic, PD pharmacodynamic, DPK dermatopharmacokinetic, WHO World Health Organization

^a Jurisdictions whose regulatory authorities had very limited information available

^b BE studies with PK endpoints are mainly required for safety reasons. Please refer to Table IV for additional details

^c *In vitro* endpoint studies may be required as supportive evidence for other *in vivo* BE studies or waiver requests by various jurisdictions and organizations. Please refer to Table VI for additional details

of topically administered drug formulations among international jurisdictions and organizations.

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