

Guidance for Industry

Topical Dermatological Drug Product NDAs and ANDAs — In Vivo Bioavailability, Bioequivalence, In Vitro Release, and Associated Studies

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
June 1998
BP #

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98D-0388

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Topical Dermatological Drug Product NDAs and ANDAs — In Vivo Bioavailability, Bioequivalence, In Vitro Release, and Associated Studies

I. INTRODUCTION

This guidance provides recommendations to sponsors and applicants who intend to provide, during either the pre- or postapproval period, information on bioavailability (BA) and bioequivalence (BE), and chemistry, manufacturing and controls in support of a new drug application (NDA), an abbreviated new drug application (ANDA), or a supplement for topical dermatological drug products. Topical dermatologic drug products belong to a class termed locally acting drug products.

II. BACKGROUND

Applicants submitting an NDA under the provisions of section 505(b) in the Federal Food, Drug & Cosmetic Act (the Act) are required to document BA (21 CFR 320.21(a)). If approved, an NDA drug product may subsequently become a reference listed drug (RLD). Under section 505(j) of the Act, a sponsor of an ANDA must document first pharmaceutical equivalence and then BE to be deemed therapeutically equivalent to a reference listed drug. Defined as relative BA, BE is documented by comparing the performance of the generic (test) and listed (reference) products.

As stated at 21 CFR 320.24, approaches to document BA/BE in order of preference are (1) pharmacokinetic (PK) measurements based on measurement of an active drug and/or metabolite in blood, plasma, and/or urine; (2) pharmacodynamic (PD) measurements; (3) comparative clinical trials; and (4) in vitro studies. For topical dermatological drug products, PK measurements in blood, plasma, and/or urine are usually not feasible to document BE because topical dermatologic products generally do not produce measurable concentrations in extra

¹This guidance has been prepared by the Topical Dermatological Drug Products Working Group of the Biopharmaceutics Coordinating Committee in the Center for Drug Evaluation and Research at the Food and Drug Administration. This guidance document represents the Agency's current thinking on methods to assess BA/BE of topically applied dermatological drug products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

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cutaneous biological fluids. The BA/BE determination for these products is thus often based on PD or clinical studies. An additional approach considered in this guidance is to document BA/BE through reliance on measurement of the active moiety(ies) in the stratum corneum. This approach is termed dermatopharmacokinetics (DPK). Although measurement of the active moiety(ies) in blood or urine is not regarded as an acceptable measurement of BA/BE for dermatological drug products, it may be used to measure systemic exposure.

III. INACTIVE INGREDIENTS

A. Safety Studies

During the IND process for an NDA, the safety of inactive ingredients in a topical drug product should be documented by specific studies or may be based on a prior history of successful use in the same amount administered via the same route of administration in an approved product. The requisite safety studies to establish the safety of a new excipient during the investigational new drug (IND) process should be discussed with appropriate review staff at the FDA. For an ANDA, the safety of inactive ingredients in an ANDA can be based on a prior history of successful use in an NDA or ANDA. If the inactive ingredients in an ANDA are not the same as the reference listed drug, the applicant should demonstrate to the Agency that the changes(s) do not affect the safety and/or efficacy of the proposed drug product. In some instances, a comparative bioavailability study will satisfy this recommendation. If preclinical or clinical studies are needed to demonstrate the safety of inactive ingredients(s) in the generic drug product, the ANDA may not be approved. In this circumstance, the applicant may wish to resubmit their application as an NDA under the provisions of 505(b)(1) or (b)(2) of the Act.

B. Waiver of Bioequivalence

In accordance with 21 CFR 314.94 (a) (9) (v), generally, the test (generic) product intended for topical use must contain the same inactive ingredients as the RLD. For all topical drug products intended for marketing under an abbreviated application, documentation of in vivo bioequivalence is required under 21 CFR 320.21 (b). For a topical solution drug product, in vivo bioequivalence may be waived if the inactive ingredients in the product are qualitatively (Q_1) identical and quantitatively (Q_2) essentially the same compared to the listed drug. In this setting, quantitatively *essentially the same* means that the amount/concentration of the inactive ingredient(s) in the test product cannot differ by more than ± 5 percent of the amount/concentration of the listed drug. Where a test solution differs in Q_1 and/or Q_2 from the listed drug, in vivo BE may be waived, provided the sponsor submits evidence that the difference does not affect

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safety and/or efficacy of the product at the time a waiver is requested.

IV. BIOAVAILABILITY AND BIOEQUIVALENCE APPROACH

A. Clinical Trial Approaches

For a drug product where information is submitted in an NDA, clinical trials may establish not only the safety and efficacy of a topical dermatological drug product but also its bioavailability in accordance with 21 CFR 320.24. Usually, this documentation is provided in relationship to the clinical trial batches used in the pivotal clinical trials. Where issues of bioequivalence during the IND phase arise during the preapproval period for a topical drug product, particularly between the pivotal clinical trial batch(es) and to be marketed formulation, application of approaches, as delineated in the FDA guidance for industry, *SUPAC-SS Nonsterile Semisolid Dosage Forms, Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation* (May 1997), may be useful. For an NDA preapproval, or for an NDA or ANDA postapproval, when other approaches are not possible, BE based on comparative clinical trials may be important. Comparative clinical trials are generally difficult to perform, highly variable, and insensitive. For these reasons, other approaches, such as dermatopharmacokinetic or pharmacodynamic, described below, may be used for BE determination.

B. Dermatopharmacokinetic Approaches²

The dermatopharmacokinetic (DPK) approach is comparable to a blood, plasma, urine PK approach applied to the stratum corneum. DPK encompasses drug concentration measurements with respect to time and provides information on drug uptake, apparent steady-state levels, and drug elimination from the stratum corneum based on a stratum corneum concentration-time curve (Maibach 1996, Shah and Maibach 1993).

When applied to diseased skin, topical drug products induce one or more therapeutic responses, where onset, duration, and magnitude depend on the relative efficiency of three sequential processes, namely, (1) the release of the drug from the dosage form, (2) penetration of the drug through the skin barrier, and (3) generation of the desired pharmacological effect. Because topical products deliver the drug directly to or near the intended site of action, measurement of the drug uptake into and drug elimination from

²See Shah, V.P, G.L. Glynn, A.Yacobi et al., "Bioequivalence of Topical Dosage Forms - Methods of Evaluation of Bioequivalence," workshop report, *Pharmaceutical Research*, 15, 167-171, 1998.

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the stratum corneum can provide a DPK means of assessing the BE of two topical drug products (Shah and Maibach 1993, Shah et al.,1998). Presumably, two formulations that produce comparable stratum corneum concentration-time curves may be BE, just as two oral formulations are judged BE if they produce comparable plasma concentration-time curves. Even though the target site for topical dermatologic drug products in some instances may not be the stratum corneum, the topical drug must still pass through the stratum corneum, except in instances of damage, to reach deeper sites of action (Shaefer 1996). In certain instances, the stratum corneum itself is the site of action. For example, in fungal infections of the skin, fungi reside in the stratum corneum and therefore DPK measurement of an antifungal drug in the stratum corneum represents direct measurement of drug concentration at the site of action (Pershing 1994). In instances where the stratum corneum is disrupted or damaged, *in vitro* drug release may provide additional information toward the BE assessment. In this context, the drug release rate may reflect drug delivery directly to the dermal skin site without passage through the stratum corneum. For antiacne drug products, target sites are the hair follicles and sebaceous glands. In this setting, the drug diffuses through the stratum corneum, epidermis, and dermis to reach the site of action. The drug may also follow follicular pathways to reach the sites of action. The extent of follicular penetration depends on the particle size of the active ingredient if it is in the form of a suspension (Allec 1997, Hueber 1994, Illel 1991, Shaefer 1996). Under these circumstances, the DPK approach is still expected to be applicable because studies indicate a positive correlation between the stratum corneum and follicular concentrations. Although the exact mechanism of action for some dermatological drugs is unclear, the DPK approach may still be useful as a measure of BE because it has been demonstrated that the stratum corneum functions as a reservoir, and stratum corneum concentration is a predictor of the amount of drug absorbed (Rougier 1983, 1986, 1990).

For reasons thus cited, DPK principles should be generally applicable to all topical dermatological drug products including antifungal, antiviral, antiacne, antibiotic, corticosteroid, and vaginally applied drug products. The DPK approach can thus be the primary means to document BA/BE. Additional information, such as comparative *in vitro* release data and particle size distribution of the active ingredient between the RLD and the test product, may provide additional supportive information. Generally, BE determinations using DPK studies are performed in healthy subjects because skin where disease is present demonstrates high variability and changes over time. Use of healthy subjects is consistent with similar use in BE studies for oral drug products.

A DPK approach is not generally applicable when (1) a single application of the dermatological preparation damages the stratum corneum, (2) for otic preparations except when the product is intended for otic inflammation of the skin; and (3) for ophthalmic preparations because the cornea is structurally different from the stratum corneum.

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The following three sections of the guidance provide general procedures for conducting a BA/BE study using DPK methodology.

1. Performance and Validation of the Skin Stripping Technique

DPK studies should include validation of both analytical methods and the technique of skin stripping. Since the DPK approach involves two components of validation (sampling and analytical method), overall DPK variability may be greater than with other methodologies. For analytical methods, levels of accuracy, precision, sensitivity, specificity, and reproducibility should be documented according to established procedures.³ The following summarizes a series of considerations for performing the skin stripping technique.

- a. Although the forearm, back, thigh, or other part of the body can be used for skin stripping studies, most studies are conducted on the forearm, for reasons of convenience.
- b. Care should be taken to avoid any damage with physical, mechanical, or chemical irritants (e.g., soaps, detergents, agents). Usual hydration and environmental conditions should be maintained. After washing prior to treatment, sufficient time, preferably two hours, should be allowed to normalize the skin surface.
- c. Detailed and workable standard operating procedures (SOPs) for area and amount of drug application, excess drug removal, and skin stripping methodology should be developed.
- d. The product's stability during the course of the study should be established. If the product is unstable, the rate and extent of degradation in situ over the period should be determined accurately so that a correction factor may be applied.
- e. Skin on both left and right arms of healthy subjects may be used to provide eight or more sites per arm. The size of the skin stripping area is important to allow collection of a sufficient drug in a sample to achieve adequate analytical detectability.

³See Shah, V.P., K. K. Midha, S. Dighe, et al., "Analytical Methods Validation: Bioavailability, Bioequivalence and Pharmacokinetic Studies," workshop report, *Pharmaceutical Research*, 9, 588-592, 1992.

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- f. Inter- and intra-arm variability should be assessed, and the treatment sites should be randomized appropriately.
- g. If a sponsor or applicant is using multiple investigators to conduct a single study, the reproducibility of skin stripping data between the investigators should be established.
- h. Either of the following approaches are recommended:
- A dose-response relationship between the drug concentration in the applied dosage form and the drug concentration in the stratum corneum should be established using the skin stripping method. A DPK dose-response relationship is analogous to a dose proportionality study performed with solid oral dosage forms. This type of study can be readily performed using three different strengths of the formulations. These can be marketed or specially manufactured products. Alternatively, a solution of the active drug representing three concentrations can be prepared for this purpose. Amount of drug in the stratum corneum at the end of a specified time interval, such as three hours, can provide a dose response relationship.
- or
- The skin stripping method should be capable of detecting differences of ± 25 percent in the strength of a product. This can be determined by applying different concentrations (e.g., 75%, 100%, 125%) of a test dosage form such as a simple solution to the skin surface for a specified exposure time such as three hours, executing the skin stripping method, and performing the appropriate statistical tests comparing the strength applied to the measured drug concentration in the stratum corneum.
- i. Using the reference product, the approximate minimum time required ($T_{\text{max-ss}}$) for drug to reach saturation level in the stratum corneum should be determined. This study establishes the time point at which the elimination phase of the study may be initiated.
- j. The drug concentration-time profile may vary with the drug, the drug potency class, formulation, subject, sites of application, circadian rhythm, ambient temperature, and humidity. These factors should be

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considered and controlled as necessary.

k. Circadian rhythms may be present and may affect the measurement of skin stripping drug concentration if the drug is also an endogenous chemical (e.g., corticosteroid or retinoic acid). In such circumstances, the baseline concentration of the endogenous compound should be measured over time from sites where no drug product has been applied.

An example of a pilot study, which incorporates the above considerations, follows.

Pilot Study

The reference drug product is randomly applied to eight sites on one forearm, with skin stripping performed at incremental times after application (e.g., 15, 30, 60 and 180 minutes). One site is used for each time point. Four additional sites at 180 minutes on the same arm should be assessed to provide a total of five replicates for the same time point. An additional site with no application of a drug product should be sampled as a control, yielding a total of nine sampling sites. The contralateral forearm may be used to assess dose response and sensitivity relationships by applying at least three concentrations of the drug product or simple drug solution for 180 minutes in duplicates. Two additional applications of the reference drug product on the same arm should be tested for 180 minutes as well to provide additional information about inter- and intra-arm variability and reproducibility. A control site with no drug application should also be included for a total of nine sites on the contralateral arm. The pilot study should be carried out in at least six subjects. Stratum corneum samples are removed according to procedures described below and analyzed for drug concentration. Standard procedures should be followed in all elements of the study and should be carried through all subsequent studies (Figure 1).

2. DPK Bioequivalence Study Protocol

a. Protocol and Subject Selection

Healthy volunteers with no history of previous skin disease or atopic dermatitis and with a healthy, homogeneous forearm (or other) skin areas sufficient to accommodate at least eight (8) treatment and measurement sites (time points) should be recruited. The number of subjects to be

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entered may be obtained from power calculations using intra- and inter-subject variability from the pilot study. Because skin stripping is highly sensitive to specific study site factors, care should be taken to perfecting the technique and enrolling a sufficient number of subjects. The following study design is based on a crossover study design, where the crossover occurs at the same time using both arms of a single subject. A crossover design in which subjects are studied on two different occasions may also be employed. If this design is employed, at least 28 days should be allowed to rejuvenate the harvested stratum corneum.

b. Application and Removal of Test and Reference Products

The treatment areas are marked using a template without disturbing or injuring the stratum corneum/skin. The size of the treatment area will depend on multiple factors including drug strength, analytical sensitivity, the extent of drug diffusion, and exposure time. The stratum corneum is highly sensitive to certain environmental factors. To avoid bias and to remain within the limits of experimental convenience and accuracy, the treatment sites and arms should be randomized. Uptake, steady-state, and elimination phases, as described in more detail below, may be randomized between the right and left arms in a subject. Exposure time points in each phase may be randomized among various sites on each arm. The test and reference products for a particular exposure time point may be applied on adjacent sites to minimize differences. Test and reference products should be applied concurrently on the same subjects according to a SOP that has been previously developed and validated. The premarked sites are treated with predetermined amounts of the products (e.g., 5 mg/sq cm) and covered with a nonocclusive guard. Occlusion is used only if recommended in product labeling. Removal of the drug product is performed according to SOPs at the designated time points, using multiple cotton swabs or Q-tips with care to avoid stratum corneum damage. In case of certain oily preparations such as ointments, washing the area with a mild soap may be needed before skin stripping. If washing is carried out, it should be part of an SOP.

c. Sites and Duration of Application

The BA/BE study should include measurements of drug uptake into the stratum corneum and drug elimination from skin. Each of these elements is important to establish bioavailability and/or bioequivalence of two products, and each may be affected by the excipients present in the

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product. A minimum of eight sites should be employed to assess uptake/elimination from each product. The time to reach steady state in the stratum corneum should be used to determine timing of samples. For example, if the drug reaches steady-state in three hours, 0.25, 0.5, 1 and 3 hours posttreatment may be selected to determine uptake and 4, 6, 8 and 24 hours may be used to assess elimination. A *zero* time point (control site away from test sites) on each subject should be selected to provide baseline data. If the test/reference drug products are studied on both forearms, randomly selected sites on one arm may be designated to measure drug uptake/steady-state. Sites on the contralateral arm may then be designated to measure drug elimination. During drug uptake, both the excess drug removal and stratum corneum stripping times are the same so that the stratum corneum stripping immediately follows the removal of the excess drug. In the elimination phase, the excess drug is removed from the sites at the steady-state time point, and the stratum corneum is harvested at succeeding times over 24 hours to provide an estimate of an elimination phase (Figure 2).

d. Collection of Sample

Skin stripping proceeds first with the removal of the first 1-2 layers of stratum corneum with two adhesive tapes strip/disc applications, using a commercially available product (e.g., D-Squame, Transpore). These first two tape-strip(s) contain the generally unabsorbed, as opposed to penetrated or absorbed, drug and therefore should be analyzed separately from the rest of the tape-strips. The remaining stratum corneum layers from each site are stripped at the designated time intervals. This is achieved by stripping the site with an additional 10 adhesive tape-strips. All ten tape strips obtained from a given time point are combined and extracted, with drug content determined using a validated analytical method. The values are generally expressed as amounts/area (e.g., ng/cm²) to maintain uniformity in reported values. Data may be computed to obtain full drug concentration-time profiles, $C_{\max-ss}$, $T_{\max-ss}$, and AUCs for the test and reference products.

e. Procedure for Skin Stripping

The general test procedures in either the pilot study or the pivotal BA/BE study are summarized below.

To assess drug uptake:

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- Apply the test and/or reference drug products concurrently at multiple sites.
- After an appropriate interval, remove the excess drug from a specific site by wiping three times lightly with a tissue or cotton swab.
- Using information from the pilot study, determine the appropriate times of sample collection to assess drug uptake.
- Repeat the application of adhesive tape two times, using uniform pressure, discarding these first two tape strips.
- Continue stripping at the same site to collect ten more stratum corneum samples.
- Care should be taken to avoid contamination with other sites.
- Repeat the procedure for each site at other designated time points.
- Extract the drug from the combined ten skin strippings and determine the concentration using a validated analytical method.
- Express the results as amount of drug per square cm treatment area of the adhesive tape.

To assess drug elimination:

- Apply the test and reference drug product concurrently at multiple sites chosen based on the results of the pilot study.
- Allow sufficient exposure period to reach apparent steady-state level.
- Remove any excess drug from the skin surface as described previously, including the first two skin strippings.
- Collect skin stripping samples using ten successive tape strips at time intervals based on the pilot study and analyze them for drug content.

3. Metrics and Statistical Analyses

A plot of stratum corneum drug concentration versus a time profile should be constructed to yield stratum corneum metrics of C_{\max} , T_{\max} and AUC.

The two one-sided hypotheses at the $\alpha = 0.05$ level of significance should be tested for AUC and C_{\max} by constructing the 90 percent confidence interval (CI) for the ratio between the test and reference averages. Individual subject parameters, as well as summary statistics (average, standard deviation, coefficient of variation, 90% CI) should be reported. For the test product to be BE, the 90 percent CI for the ratio of means (population geometric means based on log-

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transformed data) of test and reference treatments should fall within 80-125 percent for AUC and 70-143 percent for C_{max} .

Alternate approaches in the calculation of metrics and statistics are acceptable with justification.

C. Pharmacodynamic Approaches

Sometimes topically applied dermatological drug products produce direct/indirect pharmacodynamic (PD) responses that may be useful to measure BA/BE. For example, topically applied corticosteroids produce a vasoconstrictor effect that results in skin blanching. This PD response has been correlated with corticosteroid potency and efficacy. Based on this PD response, FDA issued a guidance entitled *Topical Dermatological Corticosteroids: In Vivo Bioequivalence* (June 1995). The guidance recommends that a pilot study be conducted to assess the dose-response characteristics of the corticosteroid followed by a formal study to assess BA/BE. Topically applied retinoid produces transepidermal water loss that may be used as a pharmacodynamic measure to assess BA/BE. Sponsors interested in pursuing a pharmacodynamic approach are encouraged to adhere to the general principles recommended in the June 1995 guidance, consulting with review staff at FDA as needed.

D. In Vitro Release Approaches (Lower Strength)

This section provides recommendations on studies to assess BA/BE of lower strength(s) of topical dermatological drug products in either an NDA or ANDA when the highest strength has been studied in a suitable BA/BE study such as those described previously in this document. The recommendations in this section of the guidance are based on 21 CFR 320.22 (d) (2).

Usually only one strength of a topical dermatological drug product is available although sometimes two or, rarely, three strengths may be marketed. When multiple strengths are available, a standard practice is to create lower strengths by altering the percentage of active ingredients without otherwise changing the formulation or its manufacturing process. Topical dermatological drug products usually contain relatively small amounts of the active drug substance, usually ≤ 5 percent and frequently ≤ 1 percent. In this setting, changes in the active ingredient may have little impact on the overall formulation.

1. NDAs and ANDAs

Safety and efficacy should be documented for all strengths of topical drug products in the NDA submissions. Using some of the approaches suggested in

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this guidance, BA may also be documented for the highest strength. For lower strengths, where documentation of BA is considered important, this guidance suggests that in vitro release may be performed. Similarly, for an ANDA, when bioequivalence has been documented for the highest strength, in vitro release may also be used to waive in vivo studies to assess bioequivalence between these lower strengths and the corresponding strengths of the RLD. If this approach suggests bioinequivalence, further studies may be important.

To support the approach, either to establish BA of lower strengths in an NDA or to document BE of lower strengths in an ANDA, the following conditions are important.

- Formulations of the two strengths should differ only in the concentration of the active ingredient and equivalent amount of the diluent.
- No differences should exist in manufacturing process and equipment between the two strengths.
- For an ANDA, the RLD should be marketed at both higher and lower strengths.
- For an ANDA, the higher strength of the test product should be BE to the higher strength of RLD.

In vitro drug release rate studies should be measured under the same test conditions for all strengths of both the test and RLD products. The in vitro release rate should be compared between (1) the RLD at both the higher (RHS) and lower strengths (RLS); and (2) the test (generic) products at both higher (THS) and lower strengths (TLS). Using the in vitro release rate, the following ratios and comparisons should be made:

$$\frac{\text{Release rate of RHS}}{\text{Release rate of RLS}} \approx \frac{\text{Release rate of THS}}{\text{Release rate of TLS}}$$

The ratio of the release rates of the two strengths of the test products should be about the same as the ratio of the release rate of reference products, that is:

$$\frac{\text{Release rate of RHS} \times \text{Release rate of TLS}}{\text{Release rate of RLS} \times \text{Release rate of THS}} \approx 1.$$

Using appropriate statistical methods, the standard BE interval (80-120) for a lower strength comparison of test and reference products should be used.

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2. New Intermediate Strengths

After approval, a sponsor may wish to develop an intermediate strength of a topical dermatological drug product when two strengths have been approved and are in the marketplace. In this case, the in vitro release rate of the intermediate strength should fall between the in vitro release rates of the upper and lower strengths. Modifications of the approach described in this section of the guidance can thus be applied, providing all strengths differ only in the amount of active ingredient and do not differ in manufacturing processes and equipment.

3. Postapproval Change

Information about the application of in vitro release testing when certain postapproval changes occur for both an NDA or an ANDA is provided in the guidance for industry, *SUPAC-SS Nonsterile Semisolid Dosage Forms, Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation* (May 1997).

V. In Vitro Release: Extension of the Methodology

Drug release from semisolid formulations is a property of the dosage form. Current scientific consensus is that in vitro release is an acceptable regulatory measure to signal inequivalence in the presence of certain formulation and manufacturing changes. With suitable validation, in vitro release may be used to assess batch-to-batch quality, replacing a series of tests that in the aggregate assess product quality and drug release (e.g., particle size determination, viscosity, and rheology). Because topical dosage forms are complex dosage forms, manufacturers should optimize the in vitro release test procedure for their product in a manner analogous to the use of in vitro dissolution to assess the quality of extended release products from batch to batch. In addition, in vitro release might be used in a sponsor-specific comparability protocol to allow more extensive postapproval changes in formulation and/or manufacturing, provided that BE between two products representing the extremes of the formulation and manufacturing changes have been shown to be bioequivalent, using approaches recommended earlier in this document.

VI. Systemic Exposure Studies

To ensure safety, and, when appropriate, comparable safety, information on systemic exposure is important for certain types of topical dermatological drug products, such as retinoid and high potency corticosteroids. The degree of systemic exposure for the majority of topical dermatological drug products may be determined via standard in vivo blood, plasma, or urine PK techniques. For corticosteroids, an in vivo assessment of the HPA axis suppression test may

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provide the information. For other topical dermatological drug products, such tests may not be needed.

VII. Chemistry, Manufacturing, and Controls

In addition to the standard chemistry, manufacturing, and control (CMC) tests, the active bulk drug substance for an NDA should be studied and controlled via appropriate specifications for polymorphic form, particle size distribution, and other attributes important to the quality of the resulting drug product. To the extent possible and using compendial monographs where appropriate, sponsors of ANDAs should attempt to duplicate the specifications considered important for the RLD. Where the necessary information is not available, applicants may wish to rely on in vitro release to ensure batch-to-batch consistency. CMC guidances available from FDA are generally applicable to ensure the identity, strength, quality, purity, and potency of the drug substance and drug product for a topical dermatological drug product.

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REFERENCES

Allec, A., A. Chatelus, and N. Wagner, 1997, "Skin Distribution and Pharmaceutical Aspects of Adapalene Gel," *J Am Acad Dermatol.*, 36:S119-125.

Caron, D., C. Queille-Roussel, V. P. Shah, and H. Schaefer, 1990, "Correlation Between the Drug Penetration and the Blanching Effect of Topically Applied Hydrocortisone Creams in Human Beings," *J Am Acad Dermatol.*, 23:458-462.

Hueber, F., H. Schaefer, J. Wepierre, 1994, "Role of Transepidermal and Transfollicular Routes in Percutaneous Absorption of Steroids: in Vitro Studies on Human Skin," *Skin Pharmacology*, 7:237-244.

Illel, B., H. Schaefer, J. Wepierre and O. Doucet, 1991, "Follicles Play an Important Role in Percutaneous Absorption," *J Pharm Sci.*, 80: 424-427.

Maibach, H. I. (ed.), 1996, *Dermatologic Research Techniques*, CRC Press Inc.

Parry, G.E., P. Dunn, V.P. Shah and L.K. Pershing, 1992, "Acyclovir Bioavailability in Human Skin," *J Invest Dermatol*, 98: 856-863.

Pershing, L.K., J. Corlett, and C. Jorgensen, 1994, "In Vivo Pharmacokinetics and Pharmacodynamics of Topical Ketoconazole and Miconazole in Human Stratum Corneum," *Antimicrobial agents and chemotherapy*, 38:90-95.

Pershing, L.K., L. Lambert, E.D. Wright, et al., 1994, "Topical 0.05% Betamethasone Dipropionate: Pharmacokinetic and Pharmacodynamic Dose-Response Studies in Humans," *Arch Dermatol*, 130:740-747.

Pershing, L., B. S. Silver, G.G. Krueger, et al., 1992, "Feasibility of Measuring the Bioavailability of Topical Betamethasone Dipropionate in Commercial Formulations Using Drug Content in Skin and a Skin Blanching Bioassay," *Pharm Res.*, 9:45-51.

Pershing, L.K., L.D. Lambert, V.P. Shah and S.Y. Lam, 1992, "Variability and Correlation of Chromameter and Tape-stripping Methods with the Visual Skin Blanching Assay in Quantitative Assessment of Topical 0.05% Betamethasone Dipropionate Bioavailability in Humans," *Int J Pharmaceutics*, 86:201-210.

Rougier, A., D. Dupuis, C. Lotte, et al., 1986, "Regional Variation in Percutaneous Absorption in Man: Measurement by the Stripping Method," *Arch Dermatol Res.*, 278:465-469.

Draft - Not for Implementation

Rougier, A., M. Rallis, P. Kiren and C. Lotte, 1990, "In Vivo Percutaneous Absorption: A Key Role for Stratum Corneum/Vehicle Partitioning," *Arch Dermatol Res.*, 282:498-505.

Rougier, A., D. Dupuis, C. Lotte, et al., 1983, "In Vivo Correlation Between Stratum Corneum Reservoir Function and Percutaneous Absorption," *J. Inv. Derm.*, 81:275-278.

Schaefer, H. and T. E. Redelmeir (eds.), 1996, *Skin Barrier, Principles of Percutaneous Absorption*, Eds, Karger Publishers.

Shah, V.P., K. K. Midha, S. Dighe, et al., 1992, "Analytical Methods Validation: Bioavailability, Bioequivalence and Pharmacokinetic Studies," workshop report, *Pharmaceutical Research*, 9, 588-592.

Shah, V. P. and H. I. Maibach (eds.), 1993, *Topical Drug Bioavailability, Bioequivalence and Penetration*, Plenum Press.

Shah, V.P., G.L. Flynn, A. Yacobi, et al., 1998, "Bioequivalence of Topical Dermatological Dosage Forms - Methods of Evaluation of Bioequivalence," *Pharm Res.*, 15:167-171.

Surber, C., K-P. Wilhelm, D. Bermann and H.I. Maibach, 1993, "In Vivo Skin Penetration of Acitretin in Volunteers Using Three Sampling Techniques," *Pharm Res.*, 9:1291-1294.

U.S. Food and Drug Administration (FDA), May 1997, *SUPAC-SS Nonsterile Semisolid Dosage Forms, Scale-Up and Post Approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation*, Center for Drug Evaluation and Research (CDER).

U.S. FDA, June 1995, *Topical Dermatological Corticosteroids: In Vivo Bioequivalence*, CDER.

Pilot Study

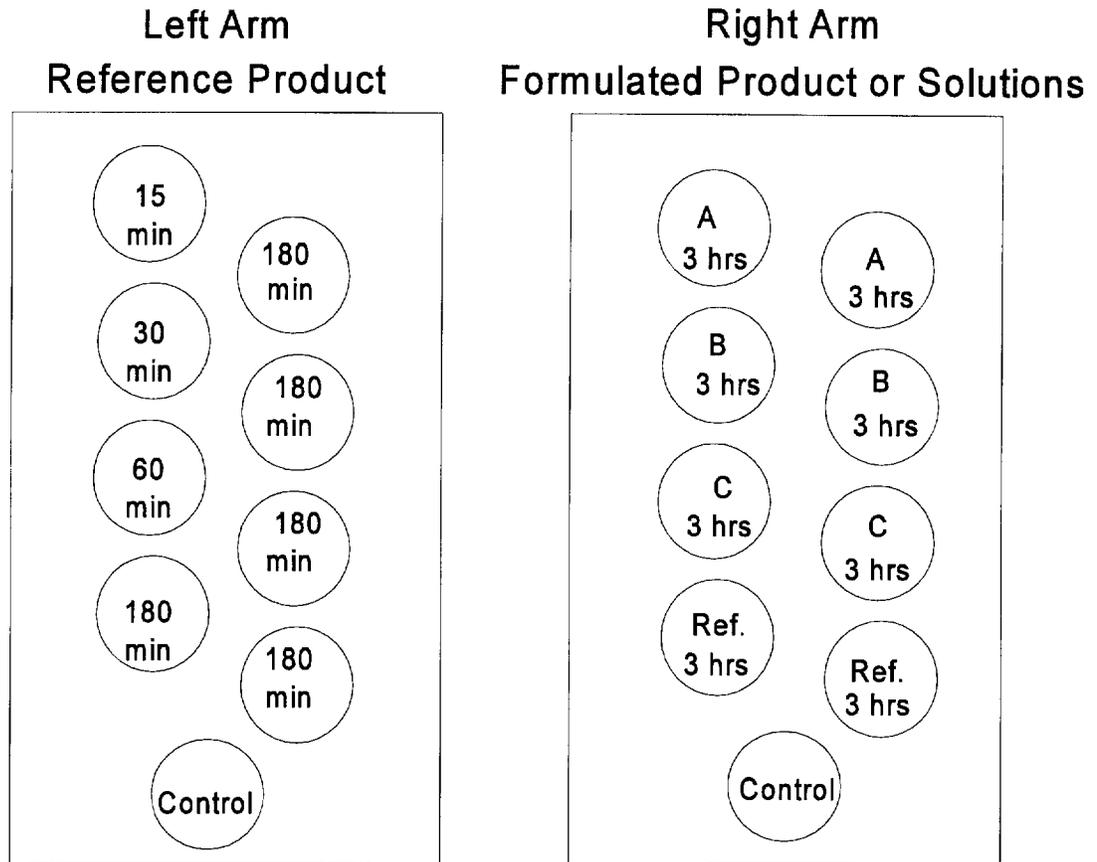


Figure 1: Schematic for drug application and removal sites for pilot study.

A, B and C represents three concentrations of the drug product or drug solution.

Bioequivalence Study

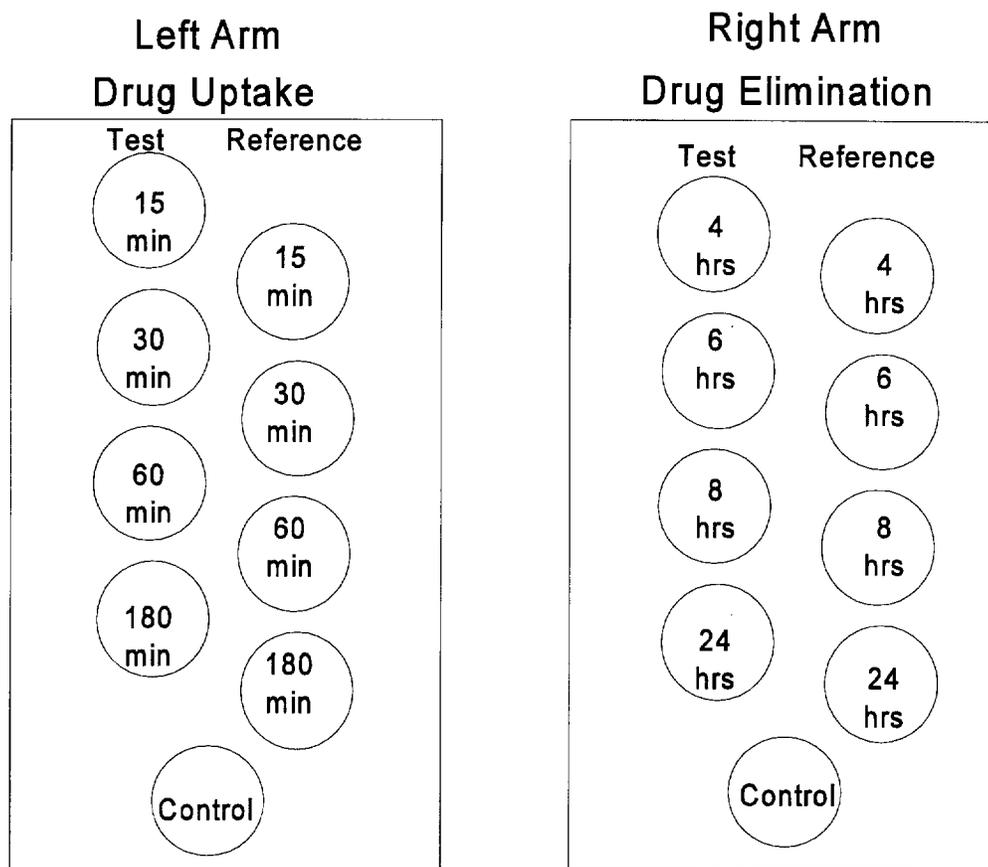


Figure 2: Schematic for drug uptake and drug elimination for bioequivalence study.