ANDA IVPT

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A. Equipment Qualification

I. Discrimination Sensitivity and Selectivity —

In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs

ANDA IVPT

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For questions regarding this draft document, contact (CDER) Susan Levine at 240-402-7936.

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Generic Drugs

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In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs

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Guidance for Industry 1 FDA CDER OGD

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

FDA FDA

I. Introduction

This guidance is intended to assist applicants who are submitting abbreviated new drug applications (A liquid-based and/or other semisolid products applied to the skin, including integumentary and mucosal (e.g membranes, which are hereinafter called "topical products." 2 Because of the complex route of delive with these products, which are typically locally acting, and the potential complexity of certain formulation products (other than topical solutions) are classified as complex products. 3 This guidance provides reco for in vitro permeation test (IVPT) studies comparing a proposed generic (test) topical product and its standard (RS) for the purpose of supporting a demonstration of bioequivalence (BE) to the reference li (RLD). The reference standard ordinarily is the RLD. 4

23 / RS ANDA ANDA IVPT lotions" RLD emulsions BE pastes UFA shampoos 2023-2027

III https://www.fda.gov/media/153631/download 21 CFR

314.3(b) ANDA FDA RS " ANDA " RS RLD

guidance does not address drug products that are administered via ophthalmic, otic, nasal, inhalation, oral, injection-based routes, or that are transdermal or topical delivery systems (including products known as pat topical patches, or extended release films). It is beyond the scope of this guidance to discuss specific topical to which this guidance applies. FDA recommends that applicants consult this guidance and any relevant pro specific guidances (PSGs) 5 and any other relevant guidances for industry, 6 when considering the des of IVPT studies that, in conjunction with other studies, as deemed necessary, may be appropriate to support demonstration that a proposed generic topical product and its RLD are bioequivalent. FDA also recommends applicants routinely refer to FDA's guidance web pages, because additional guidances may become available could assist in the development of a generic topical product.

56 FDA RLD IVPT FDA PSGs

5 Generic drug product-specific guidances are available at FDA's Product-Specific Guidances for Generic Drug Development web page https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drugdevelopment. FDA 6 ANDA

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, g describe the Agency's current thinking on a topic and should be viewed only as recommendations, unles regulatory or statutory requirements are cited. The use of the word should in Agency guidance means that s is suggested or recommended, but not required.

FDA Background This guidance has been developed as part of FDA's "Drug Competition Action Plan," 7 coordination with the Generic Drug User Fee Amendments (GDUFA) 8 program and other FDA activities, increase competition in the market place for prescription drugs, facilitate the entry of high-quality and afford generic drugs, and improve public health.

FDA" GDUFA FDA

7 See FDA Drug Competition Action Plan (describing the FDA's Drug Competition Action Plan, implemented in 2017 and designed to, things, further encourage robust and timely market competition for generic drugs), available at https://www.fda.gov/drugs/guidance regulatory-information/fda-drug-competitionaction-plan.

8 In this guidance, GDUFA refers to the generic drug user fee program codified in the Generic Drug User Fee Amendments of 2012, and Drug Administration Safety and Innovation Act (Public Law 112-144), the Generic Drug User Fee Amendments of 2017, Reauthorization Act of 2017 (Public Law 115-52), and the Generic Drug User Fee Amendments of 2022, Title III of Division F (the F Reauthorization Act of 2022) of the Continuing Appropriations and Ukraine Supplemental Appropriations Act, 2023 (Public Law 117-180

The Federal Food, Drug, and Cosmetic Act (FD&C Act) generally requires an ANDA to contain, among other th information to show that the proposed generic drug product 1) is the same as the RLD with respect to the ac ingredient(s), conditions of use, route of administration, dosage form, strength, and labeling (with certain pe differences) and 2) is bioequivalent to the RLD. 9 Thus, an ANDA will not be approved if the information s the ANDA is insufficient to show that the test product is bioequivalent to the RLD. 10

FD&C 9 ANDA 10 1 RLD RLD ANDA 2

9 See sections 505(j)(2)(A), (j)(2)(C), and (j)(4) of the FD&C Act (21 U.S.C. 355(j)(2)(A), (j)(2)(C), (j)(4)); see also 21 CFR 314.94.

10 21 CFR 314.127(a)(4), (6).

An IVPT study may be used to assess the rate and extent to which a drug (i.e., an active ingredient) from product becomes available at or near a site of action in the skin, and may be used to characterize and com rate and extent of bioavailability for a drug from a test topical product and RS. The IVPT flux profiles pharmacokinetic profiles and can be analyzed using unique IVPT endpoints that are somewhat analogo pharmacokinetic endpoints of maximum concentration (Cmax) and the area under the concentration-ti (AUC). Yet, IVPT studies characterize the rate and extent of absorption, not the distribution, metabo excretion that occurs in vivo. Therefore, while it is relevant to characterize the kinetics of topical drug bioa monitored by IVPT studies, the use in this guidance of the term "cutaneous pharmacokinetics" shoul construed to embody all aspects of pharmacokinetics—only those related to the absorption component tha

controls the rate and extent to which a topically applied drug becomes available locally at the site of ac
guidance focuses on general considerations and recommendations for the method development, method v
and conduct of IVPT studies that are submitted in ANDAs and intended to support a demonstration of BE. 11
IVPT 11 RS IVPT

11 A demonstration of no significant difference in the rate and extent of drug permeation into and through the skin of the test topica
RS using an appropriately validated IVPT method can be used to support a demonstration of BE along with other data in the applic
may be specified in a PSG), as part of a comparative product characterization-based approach. ANDA IVPT

III. IVPT method developmen IVPT

The development of an IVPT method that is suitable to support a demonstration of BE for a specific topica
routinely involves a systematic series of exploratory studies. Inappropriate or insufficient efforts to develo
method that is suitable for its intended purpose increases the likelihood that the subsequent IVPT validat
and pivotal studies will ultimately be inadequate to support a demonstration of BE. By contrast, approp
systematic IVPT method development studies help to identify IVPT study designs and protocol (method) pa
which reliably produce flux profiles that can facilitate a comparison of the cutaneous pharmacokinetics
delivered topically to the skin from test topical products and RSs.
BE IVPT IVPT IVPT BE

A detailed and well-organized IVPT method development report should be submitted in an ANDA to show
IVPT method was optimized, and to support a demonstration that the method parameters selected for the
appropriate or necessary, particularly in situations where the method parameters are different from the
recommended in this guidance). The Agency's interest in reviewing the method development report is to ur
why specific IVPT method parameters were selected and whether the resulting IVPT method is suitably sen
reproducible. This method development report should clearly indicate/distinguish the method parameters
each set of data, illustrate the efforts made to optimize the IVPT method, and demonstrate that the
parameters selected for the IVPT are appropriate.
ANDA IVPT IVPT IVPT IVPT

Applicants are encouraged to use the recommendations in this guidance, and if an applicant elects to use
that are different from those recommended in this guidance, the IVPT method development repo
demonstrate why it is scientifically justified to use an alternative approach than what is recommende
guidance to optimize the IVPT method.12 Some examples of recommended procedures are described in s
sections, to help applicants identify circumstances when information should be submitted in the ANDA t

why a different procedure was utilized.

12 IVPT ANDA IVPT

12 Applicants may choose to use an approach different from the approach recommended in this guidance. However, the alternat must comply with relevant statutes and regulations. See 21 CFR 10.115(d).

A. IVPT Method Parameters IVPT

All relevant parameters of the final IVPT method should be summarized (e.g., in a table) and submitted in t Also, information should be provided to briefly explain the choice of the final IVPT method parameter equipment (e.g., a vertical diffusion cell (VDC)), skin source (e.g., cadaver), skin type (e.g., posterior to preparation (e.g., dermatomed), skin barrier integrity test (e.g., trans-epidermal water loss (TEWL) meas skin barrier integrity test acceptance criteria (e.g., < 15 grams/meter2/hour (g/m2/hr)), topical product dos (e.g., 15 milligrams/centimeter2 (mg/cm2)), dose duration (e.g., 6 hours), study duration (e.g., 24 hours, etc.), receptor solution sampling times (e.g., 1, 2, 4, 6, 8, 12, 16, 20, and 24 hours), etc.

IVPT ^{2}/h ANDA 15 ^{2} / 15mg/6cm IVPT 24 48 VDC2

B. IVPT Method Considerations IVPT

The choice of some IVPT method parameters like the equipment, skin source, skin type, skin preparation barrier integrity test procedures may be based upon investigator experience or convenience, like the ava specific equipment or instrumentation in a laboratory, established tissue supply agreements, or other considerations. However, if the chosen IVPT method parameters do not appear to be well-suited for a spe method, it is the applicant's responsibility to systematically evaluate alternative method parameters, and u to validate that the IVPT method parameters chosen are suitable for the intended purpose. The recor procedures for IVPT method validation are detailed in section IV of this guidance.

IVPT

The choice of other IVPT method parameters like the topical product dose amount, dose duration, study (which may be longer than the dose duration), sampling schedule, sampling procedures, receptor composition, and sample analytical method may be different for each IVPT method, and such paramete methods should be systematically developed, optimized, and/or validated for the relevant topical pr appropriate. The IVPT method development studies should characterize how differences in these parameters influence the resulting IVPT flux profile so that optimal study conditions can be objectively sele among those evaluated.

IVPT IVPT

The selection of the dose amount used in the study should be assessed for each IVPT method based upo performed during IVPT method development. Different dose amounts may be compared in parallel on rep sections from the same set of donors to optimize the dose amount for the IVPT study. Considerations for se optimal dose amount may include (1) the consistency with which the dose can be applied (potentially using dispensing and/or spreading techniques), (2) the reproducibility of the flux profiles, (3) the influence of dos and dose duration on the shape of the flux profile, and (4) the approximate range of drug concentrations in solution samples at different time points (relative to the sample analytical method limits of quantification).

IVPT IVPT IVPT

The selected sampling schedule and study duration should be sufficient to characterize the c pharmacokinetics of the drug, which ideally includes a sufficiently complete flux profile to identify the m (peak) flux and a decline in the flux thereafter across multiple subsequent time points. A dose that remai skin for the duration of the study may continue to deliver the drug for a sustained period and may not n exhibit a suitable decline in the flux at later time points. In such instances, it may be appropriate to develo method that involves wiping off the applied dose after a suitable duration on the skin and continuing to m receptor solution for an extended period thereafter, during which the decline in the flux profile can be char The sampling frequency should be selected to provide a suitable resolution for the flux profile, and a mi eight non-zero sampling time points is recommended across the study duration (e.g., 48 hours).

C. IVPT Method Procedures and Controls IVPT

Suitable technical procedures and control parameters should be established during method developme may include procedures for preparing and mounting the skin on the diffusion cell in a consistent determining the instrument settings that regulate the skin surface temperature within the specifie performing the barrier integrity test appropriately, controlling the accuracy and precision of the dose dispensed on each skin section.

For example, a dosing procedure may be developed that uses a positive displacement pipette to dispense a volumetrically controlled amount of a topical product, targeting the deposition on the skin of a certain mass mg/cm^2) of topical product. If the inner diameter of the orifice in the dosing compartment of the diffusion ce millimeters (mm), and the effective dose area is ~1.77 cm^2, this would indicate a target dose of ~26.5 mg of t product per diffusion cell. Experiments during method development may establish that, based upon the den the topical product, a specific volumetric setting on a specific model of positive displacement pipette with a s pipette tip repeatedly dispenses ~27.5 mg of topical product (e.g., characterized by multiple replicate pipette

dispensations into a weigh boat on a fine balance). This pipette setting may be optimal for a dosing procedu the dose spreading instrument, like the flat bottom of a high performance liquid chromatography (HPLC) gla the rounded end of a glass rod or capillary tube, is subsequently used to spread the dispensed dose evenly skin section mounted in the diffusion cell, and where repeatedly weighing the dose-spreading instrument be after the dose spreading indicates that the residual topical product remaining on the bottom of the glass via the dose spreading reproducibly amounts to ~1.0 mg of topical product (indicating that ~26.5 mg of the topi product would reproducibly be dosed to each skin section). Such characterizations of the technical procedur control parameters for the IVPT method, like the reproducibility of the dosing procedure, should be establish during method development and may not need to be demonstrated thereafter each time the same procedu used. ^{2} 15mm 1.77cm2 26.55mg/cm

D. IVPT Skin Barrier Integrity Testing: Common Methods IVPT

The technical procedures for the skin barrier integrity test should be established during IVPT method deve Three types of barrier integrity tests are common, however, there are currently no applicable compendial protocols or acceptance criteria for any of these three types of human skin barrier integrity tests. Nor recommended parameters for the three common types of barrier integrity tests are discussed below.

IVPT

1. Trans-Epidermal Water Loss Skin Barrier Integrity Test

A TEWL skin barrier integrity test involves a measurement near the outer surface of the skin of the rate water (vapor) is fluxing through the skin barrier from the underside of the skin section. For the test, the skin mounted in a diffusion cell (e.g., clamped in place between the donor and receptor compartments), underside of the skin in contact with the receptor solution in the receptor compartment (e.g., phosphate saline, pH 7.4), and equilibrated to a skin surface temperature of 32°C ± 1°C. If skin sections are cut large e cover the flange of the diffusion cell in which they are mounted, then after they have equilibrated for severa a skin surface temperature of 32°C ± 1°C, it may be feasible to gently remove the donor compartmen disrupting a skin section's adherence to the lower flange of the diffusion cell, thereby allowing the TEWL pr placed directly on the skin surface, instead of being placed atop the donor compartment. Typically, a mi three replicate measurements are made on each skin section, which are recorded after the measureme stabilized.

TEWL

Commercially available devices to measure TEWL may differ in design and operational principles. The TEWL measured by devices with certain designs (e.g., an open chamber versus a closed chamber) may be relatively susceptible to the influence of environmental conditions. Therefore, environmental temperature and humid typically controlled as precisely as possible (e.g., a temperature range of 21°C ± 2°C and a humidity range of

20% relative humidity are ideal, if feasible). More precise control of the relative humidity (e.g., in the range o 50%) may reduce the variability of TEWL measurements for devices with certain designs. Certain designs of measurement probes and adapters for in vitro use are available by the manufacturers of TEWL devices, and appropriate to use. Inconsistency in the diameters for the measurement probe chamber, the measurement orifice, the in vitro adapters, and the skin area being measured, as well as variation in the distance of the pr sensor(s) from the skin surface, potentially because of the (variable) height of donor compartments (when applicable), could increase the variability of TEWL measurements. Inconsistent control of the alignment of th measurement device in relation to the donor compartment and/or the skin section may also increase the va of TEWL measurements. Also, the TEWL measured by devices with certain designs may be relatively more su to the influence of heat transfer from the hand that holds the probe. Applicants should follow relevant instru the manufacturer's user manual for the specific TEWL measurement device used. TEWL

20%RH 40%RH 50%RH TEWL TEWL

No more than approximately 15 grams of water per square meter per hour (i.e., ≤15g/m ^{2}/hr)could be a reas skin barrier integrity acceptance (cutoff) criterion for a TEWL barrier integrity test on human torso or thigh sk was selected as the cutoff criterion, skin sections with a TEWL> 15g/m ^{2}/hr would fail the test. Skin sections t barrier integrity test should not be dosed, but may serve as non-dosed control skin sections. A higher cutoff g/m^2/hr) may also be reasonable if justified by experimental data demonstrating that the selected acceptanc criterion appropriately discriminates skin sections with a compromised barrier integrity from those with a co barrier integrity.

TEWL ^{2}/hr ^{2}/hr TEWL 15g/m ^{2}/hr 15g ≤15g/m

However, TEWL measurements for skin sections with a competent barrier integrity can vary depending upon TEWL measurement device, the manner in which it is operated, and the environmental conditions (e.g., high ambient humidity or greater distance from the skin surface may decrease the value of the TEWL measureme Precise control of environmental and device/operational factors can minimize variability in TEWL measurem Therefore, the technical procedures for measuring TEWL should be optimized during IVPT method developm based upon prior optimization in the laboratory performing the test). Also, the TEWL measurement device sh appropriately calibrated (by the manufacturer, and for some devices, also before each set of tests). Applican provide information about the relevant calibration procedures specified by the manufacturer for the specific device used; this can be submitted in the ANDA along with the IVPT method development report, to support appropriateness of the technical procedures established by the laboratory for TEWL measurements. When a barrier integrity test is used in any study phase (IVPT method development, pilot study, validation, and/or piv study) the ambient laboratory temperature and humidity during the TEWL barrier integrity test should be m and reported.

TEWL TEWL TEWL /

2. Tritiated Water Skin Barrier Integrity Test

An example of a recommended approach to a tritiated water skin barrier integrity test would be to mount t a diffusion cell (e.g., clamped in place between the donor and receptor compartments) and allow it to equili

skin surface temperature of 32°C ± 1°C with the stratum corneum exposed to the air in the donor compart
the underside of the skin in contact with the receptor solution (e.g., phosphate buffered saline, pH 7.4).

PBS pH7.4

A small amount of tritiated water (sufficient to cover the entire surface of the skin section) would be briefly c
the stratum corneum. This dose of tritiated water would be left on the surface for a precisely controlled and
brief period (e.g., 5 minutes) after which it would be removed from the skin surface (e.g., using a pipette to r
the bulk volume and then an absorbent low lint laboratory tissue to gently blot dry). The receptor solution w
then be sampled at a precise duration after the removal of the tritiated water from the skin surface (e.g., 30
after the removal of the 5-minute dose of tritiated water from the skin surface).
While the entire volume of the receptor compartment may be removed and replenished, typically only an ali
the receptor solution (e.g., phosphate buffered saline, pH 7.4) is transferred to a suitable volume of scintillat
for counting. The volume of the aliquot typically depends upon the type of scintillation fluid used and the ma
amount of aqueous fluid that is suitable to mix with the scintillation fluid. A scintillation counter is then used
quantify the amount of radioactivity in the aliquot sampled, which can be used to calculate the amount of tri
water that permeated into the larger (entire) volume of receptor solution; the calculation is performed using
specific activity of the tritiated water to equate a given amount of radioactivity to the equivalent volume of tr
water that permeated per square centimeter of skin surface area. PBS pH7.4
Approximately 1.5 equivalent (eq.) microliter (µL) of tritiated water per cm^2 (i.e., ~1.5 eq. µL/cm^2 or ~1.5 eq.
would be a reasonable skin barrier integrity acceptance (cutoff) criterion for a tritiated water barrier integrity
involves a 5-minute dose followed by a 30minute sampling duration (i.e., sampling 30 minutes after dose rem
human torso or thigh skin. Skin sections with a tritiated water test result of > 1.5 eq. mg/cm^2 would fail the t
be excluded from the population of skin sections dosed with the topical product; skin sections that fail a barr
integrity test should not be dosed, but may serve as non-dosed control skin sections. Other acceptance crite
also be reasonable if justified by experimental data demonstrating that the selected acceptance criterion
appropriately discriminates skin sections with a compromised barrier integrity from those with a competent
integrity. ^{2} or ~1.5 eq.mg/cm5 ^{2} 30 ^{2} 135 eq.mg/cm
When calculating the results for a tritiated water barrier integrity test, it may be important to account for the
area dosed. For example, if using an acceptance criterion of 1.5 eq. mg/cm^2 with a diffusion cell that has an
diameter of 15 mm and a skin surface area of 1.77 cm^2, the mass of tritiated water that would be calculated
permeated into the receptor compartment would be ~2.7 eq. mg/cm^2 of tritiated water. 2
2 2 2.7 eq. mg/cm

3. Electrical Based Skin Barrier Integrity Tests /

There are several variations of electrical based skin barrier integrity tests that report the test result as a mea
the resistance, conductance, or a related electrical concept that characterizes the bulk flow of electrical curre

across the skin. Transepithelial electrical resistance tests involving the skin may be referred to more specific
Trans-Epidermal Electrical Resistance (TEER) skin barrier integrity tests. The test results may be described in
conductance, which is the reciprocal of resistance. Electrical based skin barrier integrity tests often use instr
that are designed to measure the inductance (L), capacitance (C), and resistance (R) of electronic circuits or e
components; these instruments are commonly known as LCR meters and have different settings (test param
that can be adjusted. / TEER

An example of a recommended approach to a TEER skin barrier integrity test would be to mount the skin in
diffusion cell (e.g., clamped in place between the donor and receptor compartments) and allow it to equilibra
skin surface temperature of 32°C ± 1°C with the stratum corneum exposed to the air in the donor compartm
the underside of the skin in contact with an ionic solution (e.g., phosphate buffered saline, pH 7.4).

TEER PBS pH7.4

A small amount of the ionic solution (sufficient to cover the entire surface of the skin section) would be brief
on the stratum corneum. Then, one lead/electrode from an LCR meter would be placed in contact with the s
the receptor compartment while the other lead/electrode would be placed in contact with the solution in the
compartment. After measuring the resistance across the skin (e.g., in kΩ, normalized for area, noting that re
is inversely proportional to area) the solution in the donor compartment would be removed and the skin sur
would be gently blotted dry with an absorbent low lint laboratory tissue. The skin (still mounted in the diffus
would then be allowed to equilibrate with the dry air above for a sufficient duration to normalize the hydrati
of the stratum corneum before being dosed with the test topical product or RS.

The results for a TEER skin barrier integrity test can vary substantially depending on the LCR meter settings (
frequency) and the technical procedures used for the test. The acceptance criterion for a specific electrical b
barrier integrity test method may be justified by experimental data demonstrating that the selected accepta
criterion appropriately discriminates skin sections with a compromised barrier integrity from those with a co
barrier integrity.

TEER LCR /

E. IVPT Skin Barrier Integrity Testing: General Considerations IVPT

There are three general considerations for the development or adoption of technical procedures for any skin
integrity test method during IVPT method development:

The technical procedures should not irreversibly alter the skin barrier. It may be acceptable to temporarily a
hydration state of the stratum corneum by briefly depositing an aqueous solution on the surface of the skin,
as sufficient time is afforded for the hydration of the stratum corneum to normalize before dosing of the top
product. The procedure described above for a brief (e.g., 5-minute) exposure of the skin surface to tritiated w
followed by a 30-minute duration during which the hydration state of the stratum corneum is re-equilibratin
likely be appropriate. By contrast, a 30-minute exposure of the skin surface to an aqueous solution for an el
based test method, followed within 5 minutes by dosing of the topical product, may not be appropriate with
further characterization of the influence of the hydration state of the stratum corneum on the discriminatior
sensitivity of the skin to differences in topical bioavailability. Similarly, if a portable lamp were placed close to
to improve visibility while study procedures were being performed, the heat from the lamp may alter the loc

(micro)environment of the skin in a manner that is not representative of the ambient environmental conditio laboratory; this should be avoided.

The acceptance criterion should be a cutoff value for the test result, at which a skin section fails the t sections that fail a barrier integrity test should not be dosed but may serve as non-dosed control skin sections. Skin sections with a passing barrier integrity test result may be considered to have a compe barrier integrity and may be dosed. This acceptance criterion should be selected based upon an understanding of the distribution of test results (among multiple replicate skin sections from multiple for the specific barrier integrity test procedure performed with the specific type and preparation of sk conditions relevant to the IVPT pivotal studies submitted in the ANDA. The intention of the barrier int test is to identify (and exclude) skin sections whose barrier integrity (intactness) is compromised. The not to reduce the inherent variability in barrier function (permeability) in human skin that is represen real variation in the human population. Also, the relative permeability of the skin to a drug from a top product may not necessarily correlate with the permeability of the skin to water, and therefore, const the variability of the skin permeability to water (using a stricter acceptance criterion that excludes a la number of skin sections) may not necessarily reduce the variability in the IVPT study results.

The acceptance criterion should be able to discriminate skin sections with a compromised barrier int This may be demonstrated by measuring the barrier integrity of skin sections mounted and equilibra diffusion cell before and after deliberately compromising the skin barrier (e.g., by repeatedly using ad tape to strip away increasing amounts of the stratum corneum, piercing the skin several times with a gauge needle, or using other physical or chemical insults to damage the skin barrier). Based upon the acceptance criterion selected, the test result for skin sections that pass the test before being damage fail the test after the damage.

“ 30

F. Differences Between IVPT Method Development and Validation IVPT

1. Optimization of an IVPT Method Prior to Advancing to IVPT Method Validation IVPT IVPT

Different study designs and method parameters may be evaluated during the IVPT method development ph example, if the selected study parameters initially involve a dose duration of 48 hours and a study duration hours, and the flux profile is measurable, but it is not feasible to identify the maximum (peak) flux and a dec the flux thereafter across multiple subsequent time points, then it may be appropriate to evaluate other stu parameters as part of the IVPT method development. For example, a different target dose of the topical pro and/or a longer sampling duration may be evaluated. An alternate study design may involve a shorter dose

(e.g., 4–6 hours) after which the applied dose is removed from the skin, and the receptor solution continues sampled across a study duration that is sufficient to identify the maximum (peak) flux and a decline in the flu thereafter across multiple subsequent time points. While shorter dose durations can help to improve the sh IVPT flux profiles, the removal of the topical product dose from the skin surface can be challenging and often its own method development and optimization. Also, the design of sensitivity studies for such an IVPT study may require a more sophisticated understanding of IVPT studies. While reasonable efforts should be made t develop an IVPT method that produces a well-defined maximum (peak) flux and a decline in the flux thereaft multiple subsequent time points, this may not be feasible for certain topical products even with study durati hours, or, at least, may not be feasible to produce reliably in all donors. In such circumstances, the IVPT met development report should detail the systematic efforts made to optimize the IVPT method.

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2. Use of a Validated Sample Analytical Method for IVPT Method Validation IVPT

The IVPT method development studies, being exploratory in nature, are often performed using a sample method that is not validated (e.g., an HPLC or ultrahigh performance liquid chromatography (UPLC) meth involving mass spectrometry (MS)); also, IVPT method development studies are often conducted in a manr not compatible with a quality management system which would otherwise make the evidence generated s support valid conclusions. Such method development studies would not be suitable to demonstrate the vali IVPT method, or associated results. Therefore, although it may appear to be redundant, certain exp performed during IVRT method development may need to be repeated during IVPT method validati appropriate controls, like a validated analytical method and procedures that are compatible with a suitab management system.

IVPT HPLC UPLC MS IVPT

It is important to clearly segregate and consistently identify those experiments and results that were pa method development separately from those that were part of IVPT method validation. It is also imp consistently identify all relevant method parameters and experimental conditions/controls for each se results. Information in the method development report should clearly identify/distinguish when the r apparently similar sets of experiments may have been obtained using different method parameters development reports should clarify which sets of diffusion cells were run in parallel or separately (e.g., on days). In addition, the sample analytical method parameters used to analyze the samples from each se experiments should be specified, and the report should indicate whether or not the sample analytical me validated (either at the time of sample analysis or subsequently).

IVPT IVPT IVPT /

IV. IVPT method validation IVPT

When all the relevant parameters of the IVPT method have been established, a pilot study should be perfor the final IVPT method and using a validated sample analytical method. The purpose of the pilot study is t the suitability of the selected IVPT method parameters by demonstrating that the performance characteris IVPT method are appropriate to compare the cutaneous pharmacokinetics of a drug delivered topically fr product and RS. The results from the pilot study, thereby, support the systematic validation of the IVPT which proceeds as a distinct study phase following IVPT method development.

IVPT IVPT IVPT RS

The results from this IVPT pilot study can help to estimate the number of donors that may be needed to a power the IVPT pivotal study. In addition to the test topical product and RS evaluated in the pilot study, assessment should be performed with a third topical product or formulation that is known or desig different from the RS, to validate the selectivity of the IVPT method to discriminate differences in bioavaila IVPT pilot study results should be plotted with error bars, comparing the permeation profiles for the three t groups in the pilot study. Separate plots should be prepared for average flux results and average c permeation results. These data can be used to support specific IVPT method validation parameters (e.g., pe profile and range).

IVPT IVPT IVPT RS RS

A pilot IVPT study performed with multiple skin donors (e.g., 4–6 skin donors) and a minimum of four repl sections per donor per treatment group is recommended. As skin from an increasing number of donors is in the pilot study, the accuracy of the estimated number of donors needed to adequately power the IV study may improve. While skin from the same donors evaluated in the pilot study may also be used in pivotal study, the results from the pilot study should not be combined with the results from the IVPT pivotal the purpose of statistical analysis.

IVPT 4 6 4 IVPT IVPT

The equipment, methodologies, and study conditions used in the IVPT pilot study (and the eventual IV study) should be appropriately validated or qualified. If an applicant elects to use equipment, methodo study conditions that are different from those recommended in this guidance, the applicant should demons it was necessary and scientifically justified to do so. Detailed protocols and well-controlled study proce recommended to ensure the precise control of dosing, sampling, and other IVPT study parameters, a potential sources of experimental bias.

IVPT IVPT

The validation of the IVPT method should incorporate specific qualifications and controls (describe performed using a validated sample analytical method, as applicable. The qualification of an IVPT method p refers to the process of defining what attributes make it suitable to perform its function in the IVPT me example, when repeated measurements of the temperature at the surface of skin mounted in a diff demonstrate that an IVPT equipment can maintain the skin surface temperature in the range of 32°C ± results can support a demonstration that the equipment is qualified to perform its function in an IVPT m which a method parameter is the control of skin surface temperature in the range of 32°C ± 1°C across the study duration.

IVPT IVPT IVPT IVI

A. Equipment Qualification

Suitable equipment for the IVPT method includes various models of VDCs and flow-through diffusion cells. T operating principles and specific test procedures differ among the various equipment; relevant procedures f manufacturer may be used for installation, operational, and performance qualifications. The laboratory qual of each diffusion cell should, at minimum, include 1) measurements of the diffusional area of the orifices of donor and receptor compartments between which the skin is mounted, 2) the empirically measured volume receptor solution compartment in each VDC or the empirically measured outflow tube length for each flow-t diffusion cell, 3) the stability of the temperature measured at the skin surface (e.g., 32°C ± 1°C) across a relev duration (e.g., 48 hours), and 4) the rate of stirring or agitation in VDCs, or the flow rate for flow-through diff cells, as applicable.

IVPT VDCs 1

If information related to the diffusional area of the orifices and the volume of the receptor solution compart each diffusion cell is available from the manufacturer, that information should be provided for each relevant diffusion cell, in addition to the empirical measurements made by the laboratory performing the IVPT studie equipment should control the diffusion cell temperature so that the skin surface temperature is verified to b (e.g., 32°C ± 1°C) for each diffusion cell before dosing (e.g., measured by a calibrated infrared thermometer), monitored periodically throughout the duration of the experiment by repeatedly measuring the skin surface temperature of a non-dosed control diffusion cell that is run in parallel with the other replicate dosed diffusi and connected to the same water bath or thermoregulation system.

IVPT

B. Membrane (Skin) Qualification (Excised human skin is recommended as the membrane for the IVPT stud validity of each skin section dosed in the study should be qualified using an appropriate test procedure to ev the stratum corneum barrier integrity. Acceptable barrier integrity tests may be based upon tritiated water permeation, TEWL, or electrical impedance/conductance measured across the skin. The test parameters and

acceptance criteria used for the skin barrier integrity test should be justified for the specific method and instrumentation that is used during the study. The skin from all donors whose skin is included in the study s prepared in a consistent manner and dermatomed to a relatively consistent thickness, within limits specifie study protocol. The skin thickness should be measured and reported for each skin section included in the st assignment of replicate skin sections from a donor to each treatment group should be randomized, as feasi acceptable to balance the distribution of skin thicknesses in each treatment group (test topical product or R procedure specified in the study protocol

IVPT TEWL /

C. Receptor Solution Qualification

The composition and pH of the receptor solution used for the IVPT study should be qualified in relation to its compatibility with the skin as well as the stability and solubility of the drug in that receptor solution. The stab the drug in the receptor solution samples should be validated as part of the receptor sample analytical meth validation. The solubility of the drug in the IVPT receptor solution should be empirically determined in triplic illustrate that the solubility of the drug in the receptor solution exceeds the highest sample concentration in pivotal study, ideally by an order of magnitude. The solubility of the drug in the IVPT receptor solution shoul sufficient to characterize the higher amounts of drug permeating from the increased drug delivery condition evaluated in the IVPT sensitivity assessment during IVPT method validation.

IVPT pH

The inclusion of 0.1% polyoxyethylene[20]oleyl ether (also known as Oleth-20, Volpo-20, or Brij-20; CAS num 98-2) is recommended to enhance the solubility of physiological buffer based (aqueous) receptor solutions f hydrophobic drugs. If additional solubility is needed, small increases in the concentration of polyoxyethylene ether (e.g., from 0.1% or 0.2%, which is typically adequate for most hydrophobic drugs, to higher concentrati recommended, but should not exceed 6% polyoxyethylene[20]oleyl ether. Other strategies to improve the s of the drug in the receptor solution that may have the potential to alter the permeability of the skin (e.g., inc organic solvents and alcohols in the receptor solution) are not recommended and may invalidate the IVPT m

0.1%(w/v) 20 Oleth-20, Volpo-20, or Brij-20 CAS 9004-98-2

The inclusion of an anti-microbial agent in the receptor solution (e.g., ~0.1% sodium azide or ~ 0.01% gentam sulfate) is recommended to mitigate potential bacterial decomposition of the dermis and/or epidermis in th diffusion cell, regardless of the study duration. Other antimicrobial agents may also be acceptable, and if us information should be included in the ANDA to explain the reason for their selection (and for the concentrat which they were used).

0.1% 0.01% /

D. Receptor Solution Sampling Qualification

The accuracy and precision of receptor solution sample collection at each time point should be app qualified. Evidence to qualify a sampling procedure should illustrate that the sampling technique can reliabl consistent volume of the sample from the well-mixed volume of the receptor compartment at each sampl and that no artifacts are likely to be created by the sampling technique. Information should be included o the equipment manufacturer's specification for the accuracy and precision of receptor solution sampli

available.

?

For IVPT studies using a flow-through diffusion cell, it may be appropriate to qualify the lengths of tubing, associated dead volumes, to accurately calculate the lag time before a sample elutes through the tubi collected. For IVPT studies using a VDC, removal of the entire receptor solution volume and full volume rep of the receptor solution at each time point may provide optimal solubility sink conditions. The sampling aliquots of the receptor solution for an IVPT study may introduce anomalous measurements of apparently flux in certain regions of the IVPT study and produce flux profiles that are difficult to interpret.

IVPT E. Environmental Control VDC IVPT

Ambient laboratory temperature and humidity during the study should be monitored and repo environmentally controlled temperature range of 21°C ± 2°C is recommended, and a humidity range of 5 relative humidity is recommended, if feasible.

21 ±2 50%RH±20%RH

F. Permeation Profile and Range

The flux profile and cumulative permeation profile for the IVPT pilot study should be plotted across a sampling times, which corresponds to the IVPT pivotal study duration. The calculation of flux and cumula permeation is discussed in more detail below. The results of the IVPT pilot study should validate that the study parameters are suitable to adequately characterize the permeation profile (the cutaneous pharmacok the drug within the selected study duration (the range of sampling time points).

IVPT IVPT

A sufficiently complete flux profile should be adequate to identify the maximum (peak) flux and a decline i thereafter across multiple subsequent time points in the IVPT pilot study. The results of the IVPT pilot stu also validate that the sampling frequency provides suitable resolution to adequately characterize the pe profile (particularly the flux profile).

IVPT IVPT

G. Precision and Reproducibility

The flux and cumulative permeation results from the IVPT pilot study (and the eventual IVPT pivotal study) s calculated, tabulated, and reported for each diffusion cell at each time point, with summary statistics to de intra-donor average, standard deviation, and percent coefficient of variation (%CV) among replicates, as w inter-donor average, standard error, and %CV. Complete results for all data values used in the calculations s reported in a clear and organized manner, to facilitate the reconstruction of the flux and cumulative pe results. The design of the study should be detailed and clear, and data values should be clearly associ specific donors, replicates, treatment groups, time points, etc.

IVPT IVPT %CV

H. Dose Depletion

The recovery of permeated drug in the receptor solution should be characterized in each diffusion c cumulative total permeation of the drug in the receptor solution over the IVPT duration. This may be expre percentage of the nominal amount of drug in the applied dose (which may be estimated based upon the

strength of the drug in the topical product and the approximate mass of topical product dosed on the skin).

IVPT “ ”

For example, if 10 mg of a topical product containing 5% drug was dosed on the membrane, the amount
the applied dose may be estimated to be 0.5 mg (or 500 µg). If a cumulative total of 10 µg of drug diffuse
receptor solution across a 48-hour duration of the IVPT, it would be possible to estimate that the 500 µg do
have been depleted by approximately 10 µg, amounting to an approximately 2% dose depletion. The
percentage dose depletion may thereby be estimated (not accounting for skin content) and should be repor

5% 10mg 0.5mg 500µg IVPT 48 10µg 500µg

I. Discrimination Sensitivity and Selectivity —

The discrimination ability of the IVPT method may be described using two concepts: sensitivity and selec
IVPT sensitivity studies are necessarily performed during IVPT method development to establish IVPT
parameters like the dose amount, dose duration, study duration, etc. However, the analysis of the results fr
studies is qualitative in nature, and they need not be repeated during the IVPT method validation phase.

IVPT IVPT IVPT IVPT I

The IVPT sensitivity studies are typically performed toward the end of the IVPT method development phase,
purpose of these studies is to incorporate the final IVPT method parameters for the target dose and dose d
be used in the pivotal study so that the IVPT sensitivity studies can support a demonstration of the validity o
IVPT method. Therefore, IVPT sensitivity studies are described within this section of the guidance in the c
IVPT validation (rather than method development) to avoid dissociating the discussions of IVPT sensitivity
performed to establish the suitability of the final IVPT method parameters) and IVPT selectivity (which is p
once the final IVPT method parameters are established, and which is based upon the IVPT pilot stud
performed as part of the IVPT method validation). With the exception of the alternative dose amounts
durations used in the IVPT sensitivity study, it is important that the IVPT method parameters are consiste
the IVPT sensitivity, pilot, and pivotal studies (including the anatomical region specified in the study prot
posterior torso), the skin source, and skin preparation).

IVPT IVPT “ IVPT ” IVPT IVPT

1. IVPT Sensitivit

IVPT sensitivity is the ability of the IVPT method to detect changes in the cutaneous pharmacokinetics of the
function of differences in drug delivery. If the IVPT method consistently demonstrates higher and lower flu
(i.e., higher and lower values for IVPT endpoints) in response to increased and decreased drug delivery, re
(or in response to other conditions expected to increase and decrease drug delivery, respectively), the IVP
may be considered sensitive.

IVPT IVPT IVPT

There are a few potential approaches by which to produce the differences in drug delivery that can be diffe
by a suitably discriminating IVPT method. Regardless of the approach used, the differences in the IVPT pe
profiles are not necessarily expected to be specifically proportional to differences in the dose amount, dose
or product strength. For example, three-fold differences in the dose amount (even if outside the recor
target dose range) may provide distinct flux curves but may not result in three-fold differences in the IVPT

because the skin barrier may be rate-limiting both in vitro and in vivo.

IVPT IVPT

In other words, if the target dose for the pivotal IVPT study was 10 mg/cm^2, a 3-fold lower dose would be ~3 and a 3-fold higher dose would be 30 mg/cm^2; thus, an IVPT sensitivity study might compare the flux profiles 10, and 30 mg/cm^{2}doses of the topical product. Similarly, if the target dose for the pivotal IVPT study was 15 a 3-fold lower dose would be 5 mg/cm^{2}and a 3-fold higher dose would be 45 mg/cm^2; thus, an IVPT sensitiv might compare the flux profiles from 5, 15, and 45 mg/cm^{2}doses of the topical product. An IVPT sensitivity s performed with multiple skin donors (e.g., 4–6 skin donors) and a minimum of four replicate skin sections pe per treatment group is recommended.

IVPT 2 10 mg/cm 2 30 mg/cm 3 10 2 30 mg/cm IVPT 2 5 mg/cm 2 45 mg/cm 2

IVPT IVPT 4 6 4

- Modulation of Dose Amount: An IVPT method development study with different dose amounts may provide supportive evidence that the IVPT methodology is sensitive to differences in drug delivery.This approach is w to topical products that contain volatile components that evaporate from the formulation following dose app to the skin. Modulating the dose amount for such topical products effectively alters the thickness of the appl The majority of volatile components from a thinner dose will tend to evaporate more rapidly (compared to a dose), and a thinner dose will tend to deliver less drug into the skin (and/or for a shorter duration) compared thicker dose. IVPT IVPT

  Modulating the dose amount can be an effective technique to modulate differences in drug delivery for form with volatile components, like gels, lotions, and many creams. However, modulating the dose amount may n necessarily produce perceptible differences in drug delivery for topical products like petrolatum-based ointm other types of topical products that do not evaporate on the skin, or that may not experience dose-depende differences in metamorphosis that can alter the rate and extent of drug delivery.

- Modulation of Dose Duration: For many topical products, it may be more effective to modulate the dose dur instead of the dose amount, to produce differences in drug delivery and associated changes in the cutaneou pharmacokinetics of the drug.

  An IVPT method development study with a controlled dose amount (e.g., 15 mg/cm^2) dosed for different du (e.g., 2 hours, 6 hours, and 12 hours) may be well suited to provide supportive evidence that the IVPT metho sensitive to differences in drug delivery from many topical products. The scenario described in this example support an IVPT study design where a topical product dose of 15 mg/cm^2 is dosed for 6 hours (the target du the IVPT study) and then wiped off. The applied dose may be removed with a series of cotton-tipped swabs, more of which may be dry and one or more of which may be moistened (e.g., with a soap solution or water). initial (dry) swab typically removes the bulk of the dose and subsequent swabs are used to remove the resid (i.e., the residue of the topical product which may otherwise continue to deliver drug into the skin) and/or to skin.

IVPT 2 15 2h 6h 12h 2 6h IVPT IVF

To support a demonstration of the sensitivity of the IVPT study, the permeation profile produced by the targ duration for the IVPT study (e.g., 6 hours) should be compared with a shorter dose duration (e.g., 2 hours) th expected to perceptibly decrease the drug delivery, and also be compared with a longer dose duration (e.g., hours) that is expected to perceptibly increase the drug delivery. Thereby, the three dose durations compare IVPT sensitivity study are designed to produce perceptible changes in the cutaneous pharmacokinetics of the a function of differences in drug delivery, and thereby support a demonstration of the sensitivity of the IVPT

IVPT IVPT 6 2 12

The specific dose durations may be selected based upon an initial exploratory IVPT study performed during method development that characterizes the permeation profile when the dose is left on the skin for a longer duration (e.g., 24 or 48 hours). An important feature of the results from such an IVPT study is the duration of initial phase of the permeation profile, when the flux is increasing at a relatively rapid rate.

IVPT IVPT 24 48

For example, if such an exploratory study indicates that the flux increases on a steep slope until approximat hours, and then continues to deliver the drug at a gradually increasing rate thereafter, it may suggest that th permeation profile for a dose duration of longer than 12 hours (e.g., 24 hours) may not be perceptibly differe that of the 12 hour dose duration, especially when compared in a relatively small number of donors and rep (e.g., four donors with four replicates each per dose duration). It may also suggest that a 12-hour dose durat be a good choice for the longest of the three dose durations in the IVPT sensitivity study.

12 12 12 24 12

The target dose duration should be selected based upon considerations like the sensitivity of the sample ana method, the ability to produce a permeation profile that can be perceptibly discriminated from that produce longer (12 hour) dose duration, and/or the labeled use of the topical product (which may indicate that the to product should be reapplied every 4–6 hours).

12 / 4 6

The shortest of the three dose durations in the IVPT sensitivity study should be selected based upon the sen the sample analytical method and its ability to produce a permeation profile that can be perceptibly discrimi from that produced by the target (6 hour) dose duration.

IVPT 6

- Modulation of Product Strength: To validate the sensitivity, specificity, and selectivity of an in vitro release te method, altered strength formulations are routinely prepared. While it may seem convenient to use these al strength formulations in an attempt to demonstrate the sensitivity and selectivity of an IVPT method, doing s not produce the desired outcomes. There may be circumstances when this strategy may produce perceptibl different permeation profiles, however, in many instances, the resulting permeation profiles may not be per different when compared in a relatively small number of donors and replicates (e.g., four donors with four re each per topical product strength). In general, the modulation of topical product strength to support a demo of IVPT sensitivity is not recommended because it may not consistently produce the expected increase or de

drug delivery; however, in certain situations, higher and lower strength formulations (relative to the nominal of the RS) may suitably increase and decrease the drug delivery and cutaneous pharmacokinetics relative to from the nominal strength topical product.

IVRT IVPT

2. IVPT Selectivity IVPT selectivity is the ability of the IVPT method to discriminate the cutaneous pharmacoki the drug between the RS and a topical product or formulation that exhibits differences in drug delivery relat RS. The IVPT pilot study with the parallel assessment of the RS, the test topical product, and a third topical pr formulation that is known or designed to be different from the RS may provide supportive evidence that the methodology is selective for differences in drug delivery. Topical product batch information for all topical pro used in IVPT method development, validation and pilot studies, as applicable, should be submitted in the stu reports. The topical product information should include, but not be limited to, information about the batch f manufacturing date, batch size, altered manufacturing processes (if applicable) and, if available, potency and uniformity. The evaluation of inequivalence may be based upon a qualitative or quantitative comparison of t permeation profiles and/or the IVPT endpoints.

IVPT IVPT “ RS ” “ RS ” IVPT RS “ R

J. Robustness

A primary assumption related to robustness testing is that the test system performs consistently when a variables (e.g., temperature, stirring rate) are at nominal settings. A value of robustness testing is that it whether the system continues to provide a consistent output when specific variables are slightly altered qualifying operational ranges for those variables. However, the variability inherent in the permeability of hu whether in vitro or in vivo, may not be compatible with the primary assumption related to the consistency o system.

Nonetheless, results from studies during IVPT method development that appear to support the robustne IVPT method or system should be reported, if relevant. For example, an IVPT method may be robust to su variations in the stirring rate of the receptor compartment. Similarly, the permeation profile of a drug through human skin may appear to be robust to certain differences in the topical product strength. U because it may not always be feasible to validate the robustness of IVPT method parameters, IVPT study pr should be controlled as precisely as possible.

IVPT IVPT IVPT

V. Sample analytical method validation

While exploratory studies performed during IVPT method development may use an unvalidated sample anal method, it is essential that all studies conducted as part of the IVPT method validation use a validated sampl analytical method. A validated IVPT method should use a validated sample analytical method (e.g., HPLC/MS UPLC/MS). Therefore, a discussion of the sample analytical method for the IVPT method is included in this gu under this section on IVPT method validation.

IVPT IVPT IVPT IVPT

However, the study protocols and reports related to the IVPT method are distinct from those for the sample analytical method that is used to quantify drug concentrations in IVPT receptor solution samples. The validat sample analytical method, in and of itself, does not demonstrate the validity of an IVPT method. Separate an reports should be submitted for the validation of the sample analytical method (e.g., HPLC/MS or UPLC/MS) the validation of the IVPT method.

IVPT IVPT IVPT HPLC/MS

Any results from studies of the IVPT method that are performed during method development using a differe sample analytical method than that which is ultimately validated, cannot support a demonstration of the val the IVPT method. Information should be provided in the IVPT method validation report referencing the (sepa sample analytical method validation, and clearly indicate that all relevant results in the IVPT method validati were obtained using a validated sample analytical method (as opposed to a sample analytical method with c parameters than those which were validated).

IVPT IVPT IVPT

The receptor sample analysis procedures (e.g., typically involving an HPLC/MS or UPLC/MS system) should b performed using chromatography software (e.g., a chromatography data system) with audit trails, and shoul a multi-point (6–8 concentration) calibration curve with suitable quality control samples, and should be valid manner compatible with the FDA guidance for industry Bioanalytical Method Validation (May 2018).

HPLC/MS UPLC/MS 6 8 FD

The validation of the receptor sample analytical method should include relevant qualifications of dilution int applicable, as well as stability assessments with the highest relevant temperature in the receptor solution fo longest relevant duration; the highest relevant temperature may be warmer than 32°C because the tempera the receptor solution is often higher than the temperature at the surface of the skin, and the longest relevar duration may be the longest interval between sampling time points for methods in which the entire recepto is replaced at each sampling time point, or it could be longer in scenarios with only partial sampling of the re solution (e.g., 34°C for 48 hours).

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If the samples are processed in specific ways for analysis (e.g., by drying and reconstituting the receptor sam smaller volume to concentrate the sample and increase the effective analytical sensitivity, or by dilution of re solution samples into the validated curve range of the sample analytical method) those procedures should b validated (e.g., by qualifying the dilution integrity during the sample analytical method validation). The stabili drug in the receptor solution sample should be validated in a receptor solution matrix that has been expose underside of the skin in a diffusion cell under conditions relevant to the IVPT pivotal study.

VI. IVPT Pivotal study

IVPTThe IVPT pivotal study protocol should incorporate considerations relevant to BE in general.IVPT

A. Handling and Retention of Samples

BE

Refer to 21 CFR 320.38, 320.63 and the FDA guidances for industry Handling and Retention of BA and E Samples (May 2004) and Compliance Policy for the Quantity of Bioavailability and Bioequivalence Samples Under 21 CFR 320.38(c) (August 2020), as applicable, regarding considerations for retention of study drug

and to 21 CFR 320.36 for requirements for maintenance of records of BE testing. Retention samples s
randomly selected from the drug supplies received before allocating topical product units for use in an IVP
which the test topical product and RS are compared.

21 CFR 320.38 320.63 FDA BA BE 2004 5 21CFR 320.38(c) BE

B. Control of Study Procedures

Study procedures that have the potential to influence the results of the study should be appropriately c
Also, experimental observations that may have the potential to influence the interpretation of the study r
well as any protocol or standard operating procedure (SOP) deviations, should be reported.

SOP

Control of procedures related to the skin include the consistent control across the study of the skin prepara
dermatoming of skin sections) and the thickness of skin sections mounted on diffusion cells, as well as
storage conditions, including the duration for which the skin was frozen and the number of freeze-thaw
which the skin was exposed. Skin from the same anatomical location should be used from all donors
demographics (age, race, sex) should be reported for all donors. Also, the IVPT sensitivity, pilot, and pivot
should use skin from the same anatomical site; otherwise, if skin from different anatomical sites is used a
different study phases, it may not be possible for the results of the IVPT sensitivity and pilot studies to s
demonstration of the discrimination ability of the IVPT method used for the pivotal study because the
parameters would not be aligned across the respective studies. Similarly, if a non-rate-limiting support mem
used beneath the skin section (e.g., a filter membrane used in a validated IVRT method for the same topica
then it should be used in a consistent manner for the IVPT sensitivity, pilot, and pivotal studies.

Control of procedures related to the dose include the control of the area of dose appli
the dose amount, the dosing technique, the dose duration, and the blinding and randomization consistent m
for all diffusion cells in the study. Differences in dosing technique may alter the metamorphosis of the dosag
on the skin, and inconsistencies in the diameter of the area dosed on each diffusion cell may significantly inf
the dosed area and contribute to errors in the calculation of flux.

Control of procedures related to sampling include the control of sampling time precision, the sampling techn
duration of sampling and replacement of receptor solution, the sample volume or flow rate, and sample han
and storage.

Control of procedures related to the pivotal study should include a non-dosed control skin section from each
donor, which should be mounted in a diffusion cell and otherwise treated identically to the dosed skin sectio
including sampling of the receptor solution at all time points to ensure that drug concentrations monitored i
receptor solution are associated with the dose applied in the IVPT pivotal study, and not drug contamination
skin from that donor that might permeate into the receptor solution across the duration of the study. A pre-
“zero” sample collected from each diffusion cell is also recommended, which may identify potential contami
associated with each skin section and/or each diffusion cell.

IVPT

In addition, investigators should perform the IVPT validation and pivotal studies within a quality managemer that includes, but is not limited to, documented procedures for: IVPT

- Study personnel identification, training, qualification, and responsibilities
- Study management and study management personnel responsibilities
- Quality control (QC) and QC personnel responsibilities QC QC
- Quality assurance (QA) and QA personnel responsibilities QA QA
- Use of SOPs SOP
- Use of study protocols
- Use of study reports
- Maintenance and control of the study facility environment and systems
- Qualification and calibration of instruments and computerized systems
- Good documentation practices including, but not limited to, contemporaneous documentation of study proc and recording of experimental observations or deviations from procedures specified in the study protocol o relevant SOPs SOPs
- Maintenance of suitable records that facilitate the reconstruction of study events and procedures, including sample handling and storage records (e.g., sample tracking logs), audit trails for sample analysis procedures of study materials and reagents, and electronic data control

Archival of study records

C. Blinding Procedure

A detailed description of the blinding procedure should be provided in the study protocol and final re packaging of the test topical product and RS should be similar in appearance to maintain adequate blind investigator and any experimental operators.

RS

D. Randomization

The method of randomization should be described in the protocol of the IVPT study and the randomization provided, preferably in a SAS data set in .xpt format (created using the SAS XPORT procedure). It is recor that an independent third party generate and hold the randomization code throughout the conduct of the minimize bias. The applicant may generate the randomization code if not involved in the packaging and la the test topical product and RS dosed in the study. A sealed copy of the randomization scheme should be re the study site and should be available to FDA investigators at the time of site inspection to allow for verificat treatment identity of each skin section.

IVPT .xpt SAS SAS XPORT

E. Dosing

In the IVPT pivotal study, the test topical product and RS should be dosed in an alternating pattern on s diffusion cells (skin sections) from each donor. One of two dosing sequences (illustrated below) may be assigned for each donor:

a. ABABAB...

b. BABABA...

IVPT RS a. ABABAB...

b. BABABA...

F. Study Design

The IVPT pivotal study should compare the cutaneous pharmacokinetics of the drug from the test topica versus that from the RS using excised human skin with a competent skin barrier mounted on a qualified diff system. The IVPT pivotal study should use a design that directly compares the test topical product and R from the same set of donors, each with the same number of replicate skin sections per donor per treatm (dosed with either test topical product or RS topical), using the same IVPT method parameters.

IVPT RS RS

The IVPT pivotal study design, methodology, and diffusion cell equipment considerations relating to precision should be controlled as precisely as possible. For example, it may be appropriate to stagger application on successive diffusion cells and to synchronize the sampling time points with the dosing tim diffusion cell, to ensure consistent durations between dosing and sampling of all diffusion cells.

IVPT

G. Inclusion Criteria

In general, the following inclusion criteria should apply: healthy, normal, barrier-competent skin from ma female donors of at least 18 years of age. Inclusion criteria related to donor demographics (e.g., age, race, se be specified in the study protocol and demographic information should be reported for each donor. A criteria may be added by the applicant.

18 /

The skin may be harvested following excision from patients undergoing a surgical procedure or exci cadavers. A consistent source is recommended for all the skin used. The anatomical region specified in protocol (e.g., posterior torso) should be consistent for all donors whose skin is included in the study.

The study protocol should specify the inclusion (acceptance) criteria for skin sections based upon the barrie test result, which should be reported for each skin section. The study protocol should specify inclusion criter to the temperature and duration of skin storage as well as the number of freeze-thaw cycles, all of which s reported for each donor's skin. The study protocol should specify the inclusion criteria related to harvesting/processing procedures and skin thickness (e.g., dermatomed skin of 500 µm ± 250 µm thicknes the IVPT study.

IVPT / 500 µm ± 250

H. Exclusion Criteria

In general, the following exclusion criteria should apply. Skin from subjects with a known (history of) derm disease should be excluded from the study. Skin with tattoos, stretch marks, or any visible sign of abnormal be excluded from the study. Skin exhibiting a significant density of terminal hair is not recommended and s excluded from the study. Additional criteria may be added by the applicant.

While gentle washing or rinsing of the skin surface is appropriate, submerging the skin in an aqueous so more than a few minutes may damage the skin barrier and should be avoided; such skin sections should be from the study. Also, skin that has been subjected to shaving with a blade; abrasive polishing; tape-str cleansing with alcohols, solvents, or other strong solutions that could damage the skin barrier should be from the study.

Skin from donors with significant background levels of the drug or other compounds that may interfere quantification of the drug in receptor solution samples should be excluded from the study. Skin fro exhibiting a high barrier integrity test failure rate among replicate skin sections may be excluded from the s skin from an alternative donor may be used instead.

I. IVPT Endpoints IVPT

The endpoints for the IVPT pivotal study are based upon parameters that characterize the rate and extent the drug permeates into and through the skin and becomes available in the receptor solution. Specifically, t drug permeation is characterized by the flux (J) and the extent of drug permeation is characterized by cumulative amount (AMT) of drug permeated into the receptor solution across the study duration.

IVPT J

The flux (rate of drug permeation) should be plotted as J on the Y-axis in units of mass/area/time (e.g., nanog (ng)/cm^2/hr) versus time on the X-axis. Flux profiles commonly resemble plasma pharmacokinetic profiles, h it is important to distinguish that the flux is a rate, rather than a concentration. The extent of drug permeatio also be plotted, as the total cumulative amount (AMT) of drug permeated on the Y-axis in units of mass/area ng/cm^2) versus time on the X-axis.

Y- X- Y- “J” / / / /

The flux should be calculated based upon: the receptor sample concentration (e.g., 2.0 ng/mL) at each time p precise, empirically measured volume of that specific diffusion cell (e.g., 6.0 mL) which may vary between ind cells; the area of dose application (e.g., 1 cm^2); and the duration for which the receptor volume was acceptin drug. For example, if the sample exemplified here represented a 2-hour period following dosing, then J woul calculated based upon the values above as: 2 2.0 ng/mL 2 ^{2})/(2 ho ng/cm^2/hrThis flux should be calculated and reported for each diffusion cell for each sampling interval and p across the entire study duration to generate the flux profile for each diffusion cell. The rate calculated above plotted at the 2-hour time point, or at the midpoint between 0 and 2 hours (i.e., 1 hour).In addition, the AMT be calculated and reported for each diffusion cell. This cumulative amount of drug that has permeated (in to across the entire study) should be reported as the AMT endpoint, rather than using a trapezoid rule to calcu area under the flux curve.

2 0 2 1

The maximum flux (Jmax) at the peak of the drug flux profile and the AMT should both be compare locally-acting test topical products and RSs. This is somewhat analogous to the comparison of the Cmax and systemically-acting test products and RSs, inasmuch as the pair of endpoints in each case facilitates a compa

the rate and extent to which the drug from each type of product (locally-acting or systemically-acting) becom
available at the site of action.A confidence interval (CI) should be calculated for each IVPT endpoint: a. the
log-transformed maximum flux (Jmax) b. the natural log-transformed total cumulative amount (AMT) per

RSs Jmax AMT RSs Cmax AUC

b. AUC

It is the responsibility of the applicant to determine the number of donors required to adequately power
pivotal study, however, a minimum of four dosed replicates per donor per treatment group (test product
recommended.

At the completion of the study, if the number of skin replicates is the same for all donors in the test topica
and RS treatment groups in the IVPT study, a statistical analysis for a balanced design is recommende
sections or diffusion cells are excluded from the final statistical analysis because of experimental loss/issue
resulting data set is unbalanced, a statistical analysis for an unbalanced design is recommended.

IVPT RS 4

IVPT Approaches to statistical analysis of the pivotal study are described in section VIII of this guidance. Ap
provides example SAS code for determining BE with both a balanced dataset and an unbalanced dataset. Ap
provides numerical examples with simulated data sets. Appendix III provides example R code for determinin

VIII I BE SAS II III BE R

VII. Submitting information on es in an ANDA ANDA IVPT

For IVPT studies with topical products submitted in ANDAs that are intended to support a demonstration of
detailed study protocols, relevant SOPs, and detailed reports should be submitted for the IVPT method valid
(including the IVPT pilot study) and the IVPT pivotal study. In addition, a detailed report describing the IVPT m
development should be submitted. These protocols, SOPs, and reports should be submitted in module 5.3.1
electronic Common Technical Document (eCTD) and should describe experimental procedures, study contro
quality management procedures, and data analyses.

BE IVPT ANDA IVPT IVPT IVPT SOPs IVPT

Note that the study protocols, SOPs, and reports related to the IVPT method are distinct from those for the s
analytical method that is used to quantify drug concentrations in IVPT receptor solution samples (e.g., an HP
UPLC/MS method). Separate protocols and SOPs should be submitted for the sample analytical method valid
Sample analytical method development and validation reports, pilot and pivotal IVPT study sample analysis r
as well as associated SOPs and protocols relevant to the sample analysis of an IVPT study with human skin s
submitted in Module 5.3.1.4 of the eCTD.

IVPT HPLC/MS UPLC/MS IVPT SOPs SOPs