ANDA申请中递交的外用药物产品的体外渗透（IVPT）研

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

ANDA申请中递交的外用药物产品的体外渗透（IVPT）研究

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

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Generic Drugs 仿制药

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

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Guidance for Industry（注释1：指南由食品药品管理局（FDA）的医药审评与研究中心（ CDER）仿制药办公室（ OGD）起草制

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Admin (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding o the public. You can use an alternative approach if it satisfies the requirements of the applicable and regulations. To discuss an alternative approach, contact the FDA staff responsible for this gui listed on the title page.
该指南代表了 FDA 对该主题目前的看法。它并不会赋予任何人任何权利，也不会约束 FDA
或公众，如果有替代的方法能够满足法律法规的要求，可以使用替代的方法。如果想探讨替代的方法，请联系该指
FDA负责执行该指南的工作人员。

I. Introduction 绪论

This guidance is intended to assist applicants who are submitting abbreviated new drug application for liquid-based and/or other semisolid products applied to the skin, including integumentary an (e.g., vaginal) membranes, which are hereinafter called “topical products.”（注释2）Because of th route of delivery associated with these products, which are typically locally acting, and the complexity of certain formulations, topical products (other than topical solutions) are classified a products.（注释3）This guidance provides recommendations for in vitro permeation test (IVPT) comparing a proposed generic (test) topical product and its reference standard (RS) for the pu supporting a demonstration of bioequivalence (BE) to the reference listed drug (RLD). The reference ordinarily is the RLD.（注释4）
本指南旨在帮助申请人提交用于皮肤的液体和/或其他半固体产品的仿制药申请（ANDA），包括皮肤和粘膜（如阴道
（注释2）。由于这些制剂通常局部起效，具有复杂递送途径和配方，外用制剂（外用溶液除外）通常称为复杂制剂
（注释3）
。本指南为拟申报的仿制药与其对照制剂（RS）的体外渗透试验（IVPT）研究提供建议，以论证与参比制剂（RLD）
（注释4）注释2
：在ANDA申请中，本指南所述的外用制剂包括软膏剂、乳膏剂、洗剂lotions、乳剂emulsions、糊剂pastes、洗发剂shampoos、凝胶剂、混悬剂
注释3：根据仿制药使用者付费法案（GDUFA）重新授权绩效目标和2023-2027财年强化计划（常称为GDUFA
III承诺函）（参见网址https://www.fda.gov/media/153631/download）中所述的定义，除另有规定外，复杂制剂产品包括具有复杂配方（如：
注释4：根据21 CFR
314.3(b)定义，参比制剂是指作为ANDA申报中参照的FDA指定的已批准药物；对照制剂（RS）被定义为“寻求ANDA的批准必须在所需的体内生物
information/search-fda-guidance-documents.This guidance does not address drug products that are administered ophthalmic, otic, nasal, inhalation, oral, or injection-based routes, or that are transdermal or topi delivery systems (including products known as patches, topical patches, or extended release films).
本指南不适用于通过眼、耳、鼻、吸入、口服或注射途径的药品，亦不适用于经皮或局部给药系统（包括贴剂、局
It is beyond the scope of this guidance to discuss specific topical products to which this guidance a FDA recommends that applicants consult this guidance and any relevant product-specific guidances (PSGs)（注释5）and any other relevant guidances for industry,（注释6）when considering the design and of IVPT studies that, in conjunction with other studies, as deemed necessary, may be appropriate to s demonstration that a proposed generic topical product and its RLD are bioequivalent. FDA also recomme applicants routinely refer to FDA’s guidance web pages, because additional guidances may become avai that could assist in the development of a generic topical product.

本文不是讨论适用于该指南范围的特定外用制剂产品的指南。FDA建议申请人，在进行IVPT研究的设计和实施时，查
（注释5）和其他行业指南（注释6）
，同时结合其他必要的研究，以支持拟申请的仿制药与RLD的生物等效性。此外，FDA建议申请人定期查阅FDA指南网

注释5：Generic drug product-specific guidances are available at FDA's Product-Specific Guidances for Generic Drug Developmen
at https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drugdevelopment. FDA仿制药特定产品开发指南，
注释6：其他相关行业指南包括：ANDA申请中递交的外用药物产品的体外释放研究指南（2022年10月）和ANDA
申请中递交的外用药物产品的物理化学和结构（Q3）特性（2022年10月）。该指南代表了FDA对该主题目前的看法。

In general, FDA's guidance documents do not establish legally enforceable responsibilities.
guidances describe the Agency's current thinking on a topic and should be viewed only as recomme
unless specific regulatory or statutory requirements are cited. The use of the word should in Agency
means that something is suggested or recommended, but not required.
一般而言，FDA
指南性文件并非具有强制执行的法律职能。实际上，指南陈述了管理部门对某一个问题当前的看法，并且仅作为建
II. Background 背景This guidance has been developed as part of FDA's "Drug Competition Action
Plan," （注释7）which, in coordination with the Generic Drug User Fee Amendments (GDUFA)（注释8） pr
other FDA activities, is intended to increase competition in the market place for prescription drugs,
facilitate the entry of high-quality and affordable generic drugs, and improve public health.
本指南已发展为FDA"药品竞争行动计划"（注释7）的一部分，配合GDUFA（注释8）
项目和其他FDA举措，旨在促进处方药市场的竞争，促进优质和实惠的药品进入市场，提高公众医疗水平。

注释7：See FDA Drug Competition Action Plan (describing the FDA's Drug Competition Action Plan, implemented in 2017 and
among other things, further encourage robust and timely market competition for generic drugs), av
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/fda-drug-competitionaction-plan.
注释8：In this guidance, GDUFA refers to the generic drug user fee program codified in the Generic Drug User Fee Amendme
Title III, Food and Drug Administration Safety and Innovation Act (Public Law 112-144), the Generic Drug User Fee Amendme
Title III, FDA Reauthorization Act of 2017 (Public Law 115-52), and the Generic Drug User Fee Amendments of 2022, Title III
F (the FDA User Fee Reauthorization Act of 2022) of the Continuing Appropriations and Ukraine Supplemental Appropriation
(Public Law 117-180).

The Federal Food, Drug, and Cosmetic Act (FD&C Act) generally requires an ANDA to contain, among oth
things, information to show that the proposed generic drug product 1) is the same as the RLD with re
the active ingredient(s), conditions of use, route of administration, dosage form, strength, and labe
(with certain permissible differences) and 2) is bioequivalent to the RLD.（注释9）Thus, an ANDA wil
approved if the information submitted in the ANDA is insufficient to show that the test product is
bioequivalent to the RLD.（注释10）
《联邦食品、药品和化妆品法案》（FD&C法案）要求ANDA申请中应包含合适的信息，说明：1）仿制药与RLD相比，
（注释9）因此，如果ANDA中提交的信息不足以证明自制制剂与RLD具有生物等效性，则ANDA将不予批准（注释10）

注释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
314.94.
注释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 ingredien topical product becomes available at or near a site of action in the skin, and may be used to cha and compare the rate and extent of bioavailability for a drug from a test topical product and RS. flux profiles resemble pharmacokinetic profiles and can be analyzed using unique IVPT endpoints somewhat analogous to the pharmacokinetic endpoints of maximum concentration (Cmax) and the area concentration-time curve (AUC). Yet, IVPT studies characterize the rate and extent of absorption, distribution, metabolism and excretion that occurs in vivo. Therefore, while it is relevant to cha the kinetics of topical drug bioavailability monitored by IVPT studies, the use in this guidance of "cutaneous pharmacokinetics" should not be construed to embody all aspects of pharmacokinetics—o related to the absorption component that directly controls the rate and extent to which a topicall drug becomes available locally at the site of action. This guidance focuses on general considera recommendations for the method development, method validation, and conduct of IVPT studies that are in ANDAs and intended to support a demonstration of BE.（注释11）

IVPT研究可用于评估外用药物产品中药物（即活性成分）到达皮肤作用部位或附近的速率和程度，表征和评估自研 时间曲线下面积（AUC）相似。然而，IVPT研究表征的是药物吸收的速率和程度，而不是体内的分布、代谢和排泄。 （注释11）

注释11：A demonstration of no significant difference in the rate and extent of drug permeation into and through the skin topical product and RS using an appropriately validated IVPT method can be used to support a demonstration of BE along wit in the application (which may be specified in a PSG), as part of a comparative product characteri approach.在ANDA申请中，通过采用合适且经过验证的IVPT方法，说明自研外用制剂与对照制剂（RS）中药物的渗透速率和通过皮肤的量无明显

IVPT method developmen IVPT方法开发

The development of an IVPT method that is suitable to support a demonstration of BE for a specifi product routinely involves a systematic series of exploratory studies. Inappropriate or insufficien to develop an IVPT method that is suitable for its intended purpose increases the likelihood subsequent IVPT validation, pilot, and pivotal studies will ultimately be inadequate to s demonstration of BE. By contrast, appropriate and systematic IVPT method development studies help to IVPT study designs and protocol (method) parameters which reliably produce flux profiles that can f a comparison of the cutaneous pharmacokinetics of a drug delivered topically to the skin from tes products and RSs.

适用于支持特定外用制剂BE论证的IVPT方法的开发，通常需要进行一系列系统的探索性研究。不合适或不充分的IV

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

应在ANDA中提交详细且结构清晰的IVPT方法开发报告，说明IVPT方法是如何优化的，所选择的IVPT方法参数是合理

Applicants are encouraged to use the recommendations in this guidance, and if an applicant elect methods 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 recomm this guidance to optimize the IVPT method.（注释12）Some examples of recommended procedures are des subsequent sections, to help applicants identify circumstances when information should be submitte ANDA to explain why a different procedure was utilized.
鼓励申请人采用本指南中推荐的方法，如果申请人选择其他方法，应在IVPT方法开发报告中说明，采用替代的方法（注释12）
。以下部分描述了本指南中推荐方法的一些示例，以帮助申请人识别在ANDA申请中何时需要递交相关信息，解释为

注释12：Applicants may choose to use an approach different from the approach recommended in this guidance. However, the approach must comply with relevant statutes and regulations. See 21 CFR
申请人可以采用指南中没有描述的其它方法。然而，所选用的替代方法必须遵守相关法律法规要求。

A. IVPT Method Parameters IVPT方法参数
All relevant parameters of the final IVPT method should be summarized (e.g., in a table) and submitt ANDA. Also, information should be provided to briefly explain the choice of the final IVPT method p like the equipment (e.g., a vertical diffusion cell (VDC)), skin source (e.g., cadaver), skin ty posterior torso), skin preparation (e.g., dermatomed), skin barrier integrity test (e.g., trans- water loss (TEWL) measurement), skin barrier integrity test acceptance criteria (e.g., < 15 grams/me (g/m2/hr)), topical product dose amount (e.g., 15 milligrams/centimeter2 (mg/cm2)), dose duration hours), study duration (e.g., 24 hours, 48 hours, etc.), receptor solution sampling times (e.g., 1, 8, 12, 16, 20, and 24 hours), etc.
应对最终确定的IVPT方法的相关参数进行总结（如，以表格形式），并在ANDA申报资料中递交。此外，还应提供信 ^{2}/h））、上样量（如，15毫克/平方厘米（15mg/cm^2
））、剂量维持时间（如，6小时）、研究持续时间（如，24小时、48小时等）、接受液取样时间点（如，1、2、4

B. IVPT Method Considerations IVPT方法考虑因素
The choice of some IVPT method parameters like the equipment, skin source, skin type, skin prepara skin barrier integrity test procedures may be based upon investigator experience or convenience, availability of specific equipment or instrumentation in a laboratory, established tissue supply ag or other logistical considerations. However, if the chosen IVPT method parameters do not appear to suited for a specific IVPT method, it is the applicant's responsibility to systematically alternative method parameters, and ultimately, to validate that the IVPT method parameters ch suitable for the intended purpose. The recommended procedures for IVPT method validation are de section IV of this guidance.
IVPT方法参数的选择，如设备、皮肤来源、皮肤类型、皮肤处理方法和皮肤屏障完整性测试方法等，可能取决于研

The choice of other IVPT method parameters like the topical product dose amount, dose duratio duration (which may be longer than the dose duration), sampling schedule, sampling procedures, solution composition, and sample analytical method may be different for each IVPT method, and such p

of IVPT methods should be systematically developed, optimized, and/or validated for the relevant product, as appropriate. The IVPT method development studies should characterize how differences method parameters influence the resulting IVPT flux profile so that optimal study conditions objectively selected from among those evaluated.
IVPT其他方法参数的选择，如外用制剂的上样量、剂量维持时间、研究持续时间（可能比剂量维持时间长）、取样

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 skin sections from the same set of donors to optimize the dose amount for the IVPT study. Considera selecting an optimal dose amount may include (1) the consistency with which the dose can be (potentially using different dispensing and/or spreading techniques), (2) the reproducibility of profiles, (3) the influence of dose amount and dose duration on the shape of the flux profile, and approximate range of drug concentrations in receptor solution samples at different time points (re the sample analytical method limits of quantification).
应根据IVPT方法开发期间进行的研究，对每个IVPT方法中所选的上样量进行评估。可通过采用相同皮肤供体的重复

The selected sampling schedule and study duration should be sufficient to characterize the pharmacokinetics of the drug, which ideally includes a sufficiently complete flux profile to ide maximum (peak) flux and a decline in the flux thereafter across multiple subsequent time points. A remains on the skin for the duration of the study may continue to deliver the drug for a sustained p may not necessarily exhibit a suitable decline in the flux at later time points. In such instances, appropriate to develop an IVPT method that involves wiping off the applied dose after a suitable du the skin and continuing to monitor the receptor solution for an extended period thereafter, during decline in the flux profile can be characterized. The sampling frequency should be selected to suitable resolution for the flux profile, and a minimum of eight non-zero sampling time points is re across the study duration (e.g., 48 hours).
所选择的取样计划（即：取样时间点）和研究持续时间应足以表征药物的皮肤药代动力学，理想情况下应包括一个

C. IVPT Method Procedures and Controls IVPT方法程序和控制
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 consisten determining the instrument settings that regulate the skin surface temperature within the specifi performing the barrier integrity test appropriately, controlling the accuracy and precision of amount dispensed on each skin section.
在方法开发过程中，应制定合适的技术规程和控制参数，包括：采用一致的方式准备皮肤并将其安装到扩散池上；

For example, a dosing procedure may be developed that uses a positive displacement pipette to dispens volumetrically controlled amount of a topical product, targeting the deposition on the skin of a cer (e.g., 15 mg/cm^2) of topical product. If the inner diameter of the orifice in the dosing compartment diffusion cell is 15 millimeters (mm), and the effective dose area is ~1.77 cm^2, this would indicate dose of ~26.5 mg of topical product per diffusion cell. Experiments during method development may es that, based upon the density of the topical product, a specific volumetric setting on a specific mod positive displacement pipette with a specific pipette tip repeatedly dispenses ~27.5 mg of topical p

(e.g., characterized by multiple replicate pipette dispensations into a weigh boat on a fine balance) pipette setting may be optimal for a dosing procedure where the dose spreading instrument, like the bottom of a high performance liquid chromatography (HPLC) glass vial, or the rounded end of a glass capillary tube, is subsequently used to spread the dispensed dose evenly upon the skin section mounte diffusion cell, and where repeatedly weighing the dose-spreading instrument before and after the dose spreading indicates that the residual topical product remaining on the bottom of the glass vial after dose spreading reproducibly amounts to ~1.0 mg of topical product (indicating that ~26.5 mg of the to product would reproducibly be dosed to each skin section). Such characterizations of the technical pr and control parameters for the IVPT method, like the reproducibility of the dosing procedure, should established during method development and may not need to be demonstrated thereafter each time the sa procedure is used.

例如，在上样方式的研究中，可以采用外置活塞式移液器（即：移液枪）把一定体积的外用药物制剂分配到皮肤上

2

）；如扩散池供给室的孔口内径是15mm，则其有效面积约为1.77cm2，意味着每个扩散池中制剂的目标剂量约为26.5

D. IVPT Skin Barrier Integrity Testing: Common Methods IVPT皮肤屏障完整性测试：常用方法

The technical procedures for the skin barrier integrity test should be established during IVP development. Three types of barrier integrity tests are common, however, there are currently no a compendial standard protocols or acceptance criteria for any of these three types of human skin integrity tests. Nonetheless, recommended parameters for the three common types of barrier integr are discussed below.

应在IVPT方法开发期间建立皮肤屏障完整性测试方法。常用的皮肤屏障完整性测试方法有三种，但还没有相应的药

1. Trans-Epidermal Water Loss Skin Barrier Integrity Test 经皮水分散失法测试皮肤屏障完整性

A TEWL skin barrier integrity test involves a measurement near the outer surface of the skin of th which water (vapor) is fluxing through the skin barrier from the underside of the skin section. For the skin section is mounted in a diffusion cell (e.g., clamped in place between the donor and compartments), with the underside of the skin in contact with the receptor solution in the compartment (e.g., phosphate buffered saline, pH 7.4), and equilibrated to a skin surface tempe 32° C ± 1° C. If skin sections are cut large enough to cover the flange of the diffusion cell in w are mounted, then after they have equilibrated for several hours at a skin surface temperature of 1° C, it may be feasible to gently remove the donor compartment without disrupting a skin s adherence to the lower flange of the diffusion cell, thereby allowing the TEWL probe to be placed di the skin surface, instead of being placed atop the donor compartment. Typically, a minimum of three measurements are made on each skin section, which are recorded after the measurements have stabilize TEWL皮肤屏障完整性测试是通过测定皮肤外表面附近的水分（蒸汽），评估水分从皮肤下侧通过皮肤屏障的速率。

Commercially available devices to measure TEWL may differ in design and operational principles. The measured by devices with certain designs (e.g., an open chamber versus a closed chamber) may be rela more susceptible to the influence of environmental conditions. Therefore, environmental temperature humidity are typically controlled as precisely as possible (e.g., a temperature range of 21° C ± 2° humidity range of 50% ± 20% relative humidity are ideal, if feasible). More precise control of the humidity (e.g., in the range of 40% - 50%) may reduce the variability of TEWL measurements for devi certain designs. Certain designs of measurement probes and adapters for in vitro use are available b

manufacturers of TEWL devices, and may be appropriate to use. Inconsistency in the diameters for the measurement probe chamber, the measurement probe orifice, the in vitro adapters, and the skin area be measured, as well as variation in the distance of the probe sensor(s) from the skin surface, potentia because of the (variable) height of donor compartments (when applicable), could increase the variabil TEWL measurements. Inconsistent control of the alignment of the TEWL measurement device in relation donor compartment and/or the skin section may also increase the variability of TEWL measurements. Al TEWL measured by devices with certain designs may be relatively more susceptible to the influence of transfer from the hand that holds the probe. Applicants should follow relevant instructions in the manufacturer’ s user manual for the specific TEWL measurement device used.

商业化可用于TEWL测定的设备，有不同的设计和操作原理。由于设计的差异，一些TEWL测试设备可能相对更容易受 ± 2° C、湿度控制在50% RH±
20%RH范围内）。更精确的控制相对湿度（如，控制在40%RH～50%RH范围内）可以降低一些设备测定TEWL结果的变异

No more than approximately 15 grams of water per square meter per hour (i.e., ≤15g/m^2/hr)could be a reasoable skin barrier integrity acceptance (cutoff) criterion for a TEWL barrier integrity test on l torso or thigh skin; if this was selected as the cutoff criterion, skin sections with a TEWL> 15g/m^2 fail the test. Skin sections that fail a barrier integrity test should not be dosed, but may serve as dosed control skin sections. A higher cutoff (e.g., ≤20 g/m^2/hr) may also be reasonable if justifie experimental data demonstrating that the selected acceptance criterion appropriately discriminates sk sections with a compromised barrier integrity from those with a competent barrier integrity.

对于人体躯干或大腿皮肤，采用TEWL屏障完整性测试法，合理的皮肤屏障完整性接受（截止）标准是每小时每平方 ^{2}/hr）；如果选择其作为截止标准，TEWL大于15g/m^2
/hr的皮肤，则不具有皮肤完整性。未通过皮肤完整性测试的皮肤切片不应进行上样操作，但可用作为无剂量空白对 ^{2}/hr）。

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

然而，具有合格屏障完整性皮肤的TEWL测量值，可能会因TEWL测试设备、操作方式和环境条件的不同而变化（如，

2. Tritiated Water Skin Barrier Integrity Test 氚化水渗透法测试皮肤屏障完整性

An example of a recommended approach to a tritiated water skin barrier integrity test would be to skin in a diffusion cell (e.g., clamped in place between the donor and receptor compartments) and al equilibrate to a skin surface temperature of 32° C ± 1° C with the stratum corneum exposed to the a donor compartment and the underside of the skin in contact with the receptor solution (e.g., buffered saline, pH 7.4).

氚化水渗透法测试皮肤屏障完整性的一个推荐方法是，将皮肤安装到扩散池中（如，夹在供给室和接收室之间），
± 1° C。

A small amount of tritiated water (sufficient to cover the entire surface of the skin section) would
briefly dosed on the stratum corneum. This dose of tritiated water would be left on the surface for
precisely controlled and relatively brief period (e.g., 5 minutes) after which it would be removed f
skin surface (e.g., using a pipette to remove the bulk volume and then an absorbent low lint laborat
tissue to gently blot dry). The receptor solution would then be sampled at a precise duration after
removal of the tritiated water from the skin surface (e.g., 30 minutes after the removal of the 5-mi
of tritiated water from the skin surface).
将少量的氚化水（足以覆盖皮肤切片的整个表面）上样到皮肤角质层，精确控制氚化水留在皮肤表面的时间（如，
While the entire volume of the receptor compartment may be removed and replenished, typically only a
of the receptor solution (e.g., phosphate buffered saline, pH 7.4) is transferred to a suitable volu
scintillation fluid for counting. The volume of the aliquot typically depends upon the type of scint
fluid used and the maximum amount of aqueous fluid that is suitable to mix with the scintillation fl
scintillation counter is then used to quantify the amount of radioactivity in the aliquot sampled, w
be used to calculate the amount of tritiated water that permeated into the larger (entire) volume of
solution; the calculation is performed using the specific activity of the tritiated water to equate
amount of radioactivity to the equivalent volume of tritiated water that permeated per square centim
skin surface area.
虽然可以完全移取整个接收室的接收液（如PBS，pH7.4），通常情况下，移取一部分接收液转移至适当体积的闪烁
Approximately 1.5 equivalent (eq.) microliter (μL) of tritiated water per cm^2 (i.e., ~1.5 eq. μL/cm
eq. mg/cm^2) would be a reasonable skin barrier integrity acceptance (cutoff) criterion for a tritiat
barrier integrity test that involves a 5-minute dose followed by a 30minute sampling duration (i.e.,
30 minutes after dose removal) on human torso or thigh skin. Skin sections with a tritiated water te
of > 1.5 eq. mg/cm^2 would fail the test and be excluded from the population of skin sections dosed w
topical product; skin sections that fail a barrier integrity test should not be dosed, but may serve
dosed control skin sections. Other acceptance criteria may also be reasonable if justified by experi
data demonstrating that the selected acceptance criterion appropriately discriminates skin sections
compromised barrier integrity from those with a competent barrier integrity.
对于人体躯干或大腿皮肤，采用氚化水屏障完整性测试法，将氚化水上样到皮肤表面5分钟后移除，在移除30分钟后
eq. μL/cm^2 or ~1.5 eq.mg/cm^2）。采用氚化水屏障完整性测试法，如果测定结果大于1.5 eq.mg/cm^2
，则不具有皮肤完整性。未通过皮肤完整性测试的皮肤切片不应进行上样操作，但可用作为无剂量空白对照皮肤切
When calculating the results for a tritiated water barrier integrity test, it may be important to ac
the surface area dosed. For example, if using an acceptance criterion of 1.5 eq. mg/cm^2 with a diffus
that has an orifice diameter of 15 mm and a skin surface area of 1.77 cm^2, the mass of tritiated wat
would be calculated to have permeated into the receptor compartment would be ~2.7 eq. mg/cm^2 of triti
water.
对于氚化水屏障完整性测试法，在结果计算时，需要重点关注上样表面积。例如，当扩散池的直径是15mm时，相应
cm^2，如果采用1.5 eq.mg/cm^2的接受标准，则渗透进入接收室的氚化水的量应不超过2.7 eq. mg/cm^2。

3. Electrical Based Skin Barrier Integrity Tests 电阻/电导值法测试皮肤屏障完整性

There are several variations of electrical based skin barrier integrity tests that report the test r
a measure of the resistance, conductance, or a related electrical concept that characterizes the bul

electrical current across the skin. Transepithelial electrical resistance tests involving the skin ma
referred to more specifically as Trans-Epidermal Electrical Resistance (TEER) skin barrier integrity
The test results may be described in units of conductance, which is the reciprocal of resistance. El
based skin barrier integrity tests often use instruments that are designed to measure the inductance
capacitance (C), and resistance (R) of electronic circuits or electrical components; these instrumen
commonly known as LCR meters and have different settings (test parameters) that can be adjusted.
电阻/电导法测定皮肤完整性有几种变量，以电阻、电导或相关的电概念报告测试结果，用于表征流过皮肤的电流量
An example of a recommended approach to a TEER skin barrier integrity test would be to mount the skin
diffusion cell (e.g., clamped in place between the donor and receptor compartments) and allow it to
equilibrate to a skin surface temperature of 32° C ± 1° C with the stratum corneum exposed to the a
donor compartment and the underside of the skin in contact with an ionic solution (e.g., phosphate bu
saline, pH 7.4).
TEER皮肤屏障完整性测试的一个推荐方法是，将皮肤安装到扩散池中（如，夹在供给室和接收室之间），使皮肤的
A small amount of the ionic solution (sufficient to cover the entire surface of the skin section) wou
briefly dosed on the stratum corneum. Then, one lead/electrode from an LCR meter would be placed in
with the solution in the receptor compartment while the other lead/electrode would be placed in conta
the solution in the donor compartment. After measuring the resistance across the skin (e.g., in kΩ,
normalized for area, noting that resistance is inversely proportional to area) the solution in the do
compartment would be removed and the skin surface would be gently blotted dry with an absorbent low
laboratory tissue. The skin (still mounted in the diffusion cell) would then be allowed to equilibra
the dry air above for a sufficient duration to normalize the hydration state of the stratum corneum
being dosed with the test topical product or RS.
将少量的离子溶液（足以覆盖皮肤切片的整个表面）短暂的施加到皮肤角质层上；然后，将LCR仪表的一端电极与接
The results for a TEER skin barrier integrity test can vary substantially depending on the LCR meter
(e.g., frequency) and the technical procedures used for the test. The acceptance criterion for a spec
electrical based skin barrier integrity test method may be justified by experimental data demonstrati
the selected acceptance criterion appropriately discriminates skin sections with a compromised barri
integrity from those with a competent barrier integrity.
TEER皮肤屏障完整性测试的结果，可能因LCR仪表设置（如，频率）和所用的测试技术方法不同，产生很大变化。电
E. IVPT Skin Barrier Integrity Testing: General Considerations IVPT皮肤完整性测试：注意事项
There are three general considerations for the development or adoption of technical procedures for an
barrier integrity test method during IVPT method development:
在方法开发过程中，皮肤屏障完整性的任一测试方法的开发或选择，都应注意以下三个方面：
The technical procedures should not irreversibly alter the skin barrier. It may be acceptable to temp
alter the hydration state of the stratum corneum by briefly depositing an aqueous solution on the su
the skin, as long as sufficient time is afforded for the hydration of the stratum corneum to normali
dosing of the topical product. The procedure described above for a brief (e.g., 5-minute) exposure o
skin surface to tritiated water followed by a 30-minute duration during which the hydration state of
stratum corneum is re-equilibrating would likely be appropriate. By contrast, a 30-minute exposure o
skin surface to an aqueous solution for an electrical-based test method, followed within 5 minutes by
of the topical product, may not be appropriate without further characterization of the influence of
hydration state of the stratum corneum on the discrimination sensitivity of the skin to differences
topical bioavailability. Similarly, if a portable lamp were placed close to the skin to improve visi
while study procedures were being performed, the heat from the lamp may alter the local (micro)enviro
the skin in a manner that is not representative of the ambient environmental conditions in the labora

this should be avoided.
测定方法不应不可逆的改变皮肤完整性。可以接受将水溶液上样到皮肤表面后，短暂的改变角质层水合状态

The acceptance criterion should be a cutoff value for the test result, at which a skin section the test. Skin sections that fail a barrier integrity test should not be dosed but may serve a dosed control skin sections. Skin sections with a passing barrier integrity test result may be considered to have a competent barrier integrity and may be dosed. This acceptance criterion s selected based upon an understanding of the distribution of test results (among multiple repli skin sections from multiple donors) for the specific barrier integrity test procedure performe the specific type and preparation of skin under conditions relevant to the IVPT pivotal studie submitted in the ANDA. The intention of the barrier integrity test is to identify (and exclude sections whose barrier integrity (intactness) is compromised. The intent is not to reduce the variability in barrier function (permeability) in human skin that is representative of real va in the human population. Also, the relative permeability of the skin to a drug from a topical 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 a larger number of skin sections) may not necessarily reduce the variability in the IVPT study results.
接受标准应是皮肤未通过屏障完整性测试的截止值。未通过皮肤完整性测试的皮肤切片不应进行上样操作，

The acceptance criterion should be able to discriminate skin sections with a compromised barri integrity. This may be demonstrated by measuring the barrier integrity of skin sections mounte equilibrated in a diffusion cell before and after deliberately compromising the skin barrier repeatedly using adhesive tape to strip away increasing amounts of the stratum corneum, pierci skin several times with a 30 gauge needle, or using other physical or chemical insults to dama skin barrier). Based upon the acceptance criterion selected, the test result for skin sections pass the test before being damaged should fail the test after the damage.
接受标准应能够区分屏障完整性受损的皮肤切片。对于接受标准的论证，可通过“在特意破坏皮肤屏障的前

F. Differences Between IVPT Method Development and Validation IVPT方法开发和验证的区别

1. Optimization of an IVPT Method Prior to Advancing to IVPT Method V
在IVPT方法验证前进行IVPT方法的优化

Different study designs and method parameters may be evaluated during the IVPT method development pha example, if the selected study parameters initially involve a dose duration of 48 hours and a study of 48 hours, and the flux profile is measurable, but it is not feasible to identify the maximum (peak and a decline in the flux thereafter across multiple subsequent time points, then it may be appropria evaluate other study parameters as part of the IVPT method development. For example, a different targ of the topical product and/or a longer sampling duration may be evaluated. An alternate study design involve a shorter dose duration (e.g., 4 - 6 hours) after which the applied dose is removed from the the receptor solution continues to be sampled across a study duration that is sufficient to identify maximum (peak) flux and a decline in the flux thereafter across multiple subsequent time points. Whil shorter dose durations can help to improve the shape of IVPT flux profiles, the removal of the topica product dose from the skin surface can be challenging and often requires its own method development a

optimization. Also, the design of sensitivity studies for such an IVPT study design may require a mo
sophisticated understanding of IVPT studies. While reasonable efforts should be made to develop an I
method that produces a well-defined maximum (peak) flux and a decline in the flux thereafter across
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, t
method development report should detail the systematic efforts made to optimize the IVPT method.
在IVPT方法开发期间可以对不同的研究设计和方法参数进行评估。例如，如果最初选择的研究参数是剂量维持时间

2. Use of a Validated Sample Analytical Method for IVPT Method V
采用已验证的分析方法进行IVPT方法验证

The IVPT method development studies, being exploratory in nature, are often performed using
analytical method that is not validated (e.g., an HPLC or ultrahigh performance liquid chromatograp
method, often involving mass spectrometry (MS)); also, IVPT method development studies are often con
a manner that is not compatible with a quality management system which would otherwise make the
generated suitable to support valid conclusions. Such method development studies would not be su
demonstrate the validity of an IVPT method, or associated results. Therefore, although it may appe
redundant, certain experiments performed during IVRT method development may need to be repeated du
method validation, using appropriate controls, like a validated analytical method and procedures
compatible with a suitable quality management system.
IVPT方法开发研究，本质上具有探索性，通常是采用未经验证的样品分析方法（如，HPLC或UPLC，通常需要进行质

It is important to clearly segregate and consistently identify those experiments and results that
of IVPT method development separately from those that were part of IVPT method validation. It
important to consistently identify all relevant method parameters and experimental conditions/con
each set of IVPT results. Information in the method development report should clearly identify/di
when the results for apparently similar sets of experiments may have been obtained using differe
parameters. Method development reports should clarify which sets of diffusion cells were run in pa
separately (e.g., on separate days). In addition, the sample analytical method parameters used to an
samples from each set of IVPT experiments should be specified, and the report should indicate wheth
the sample analytical method was validated (either at the time of sample analysis or subsequently).
需要注意的是，应将IVPT方法开发和IVPT方法验证的试验结果分开来看，并采用一致的评价标准；对于每组IVPT结

VPT method validation IVPT方法验证

When all the relevant parameters of the IVPT method have been established, a pilot study should be
using the final IVPT method and using a validated sample analytical method. The purpose of the pilot
to validate the suitability of the selected IVPT method parameters by demonstrating that the pe
characteristics of the IVPT method are appropriate to compare the cutaneous pharmacokinetics o
delivered topically from a test product and RS. The results from the pilot study, thereby, sup
systematic validation of the IVPT method, which proceeds as a distinct study phase following IV
development.
在所有相关的IVPT方法参数确定之后，应采用最终确定的IVPT方法和已验证的样品分析方法进行初始研究。初步研

The results from this IVPT pilot study can help to estimate the number of donors that may be r adequately power the IVPT pivotal study. In addition to the test topical product and RS evaluate pilot study, a parallel assessment should be performed with a third topical product or formulation known or designed to be different from the RS, to validate the selectivity of the IVPT method to dis differences in bioavailability. The IVPT pilot study results should be plotted with error bars, comp permeation profiles for the three treatment groups in the pilot study. Separate plots should be pre average flux results and average cumulative permeation results. These data can be used to support IVPT method validation parameters (e.g., permeation profile and range).
IVPT的初步研究结果有助于评估在IVPT正式研究中所需的供体数量。在IVPT的初步研究中，除了对自研外用制剂和

A pilot IVPT study performed with multiple skin donors (e.g., 4-6 skin donors) and a minimum replicate skin sections per donor per treatment group is recommended. As skin from an increasing donors is evaluated in the pilot study, the accuracy of the estimated number of donors needed to a power the IVPT pivotal study may improve. While skin from the same donors evaluated in the pilot also be used in the IVPT pivotal study, the results from the pilot study should not be combined results from the IVPT pivotal study for the purpose of statistical analysis.
在IVPT初步研究中，建议采用多个皮肤供体（如，4～6个皮肤供体），且每个试验组的每个供体至少4个重复皮肤切

The equipment, methodologies, and study conditions used in the IVPT pilot study (and the event pivotal study) should be appropriately validated or qualified. If an applicant elects to use e methodologies, or study conditions that are different from those recommended in this guidance, the should demonstrate why it was necessary and scientifically justified to do so. Detailed protocols controlled study procedures are recommended to ensure the precise control of dosing, sampling, and o study parameters, as well as potential sources of experimental bias.
IVPT初步研究（和最终的IVPT正式研究）中所用的设备、方法和研究条件应进行合适的验证或确认。如果申请人使

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 IV parameter refers to the process of defining what attributes make it suitable to perform its functi IVPT method. For example, when repeated measurements of the temperature at the surface of skin mou diffusion cell demonstrate that an IVPT equipment can maintain the skin surface temperature in the 32° C ± 1° C, the results can support a demonstration that the equipment is qualified to per function in an IVPT method for which a method parameter is the control of skin surface temperatu range of 32° C ± 1° C across the relevant study duration.
IVPT方法验证应包括下述的确认和控制内容，如适用，使用已验证样品分析方法。IVPT方法参数确认是表征IVPT方

A. Equipment Qualification 设备确认
Suitable equipment for the IVPT method includes various models of VDCs and flow-through diffusion ce operating principles and specific test procedures differ among the various equipment; relevant proce from the manufacturer may be used for installation, operational, and performance qualifications. The laboratory qualification of each diffusion cell should, at minimum, include 1) measurements of the

diffusional area of the orifices of the donor and receptor compartments between which the skin is mou
the empirically measured volume of the receptor solution compartment in each VDC or the empirically m
outflow tube length for each flow-through diffusion cell, 3) the stability of the temperature measure
skin surface (e.g., 32° C ± 1° C) across a relevant duration (e.g., 48 hours), and 4) the rate of st
or agitation in VDCs, or the flow rate for flow-through diffusion cells, as applicable.
可用于IVPT方法的设备有VDCs（立式扩散池）和流通池。每种类型设备的操作原理和相关测定方法不同；可根据生产
If information related to the diffusional area of the orifices and the volume of the receptor solutio
compartment for each diffusion cell is available from the manufacturer, that information should be pr
for each relevant diffusion cell, in addition to the empirical measurements made by the laboratory pe
the IVPT studies. The equipment should control the diffusion cell temperature so that the skin surfac
temperature is verified to be stable (e.g., 32° C ± 1° C) for each diffusion cell before dosing (e.g
measured by a calibrated infrared thermometer), and monitored periodically throughout the duration of
experiment by repeatedly measuring the skin surface temperature of a non-dosed control diffusion cell
run in parallel with the other replicate dosed diffusion cells and connected to the same water bath o
thermoregulation system.
如果可以从生产商处获取每个扩散池的孔口扩散面积和接收室的容积信息，除了提供实验室进行IVPT研究时测定的
B. Membrane (Skin) Qualification 膜（皮肤）确认Excised human skin is recommended as the membrane for
study. The validity of each skin section dosed in the study should be qualified using an appropriate
procedure to evaluate the stratum corneum barrier integrity. Acceptable barrier integrity tests may b
upon tritiated water permeation, TEWL, or electrical impedance/conductance measured across the skin.
parameters and acceptance criteria used for the skin barrier integrity test should be justified for t
specific method and instrumentation that is used during the study. The skin from all donors whose ski
included in the study should be prepared in a consistent manner and dermatomed to a relatively consis
thickness, within limits specified in the study protocol. The skin thickness should be measured and r
for each skin section included in the study. The assignment of replicate skin sections from a donor t
treatment group should be randomized, as feasible. It is acceptable to balance the distribution of sk
thicknesses in each treatment group (test topical product or RS) by a procedure specified in the stud
protocol
建议采用离体人类皮肤作为IVPT研究用膜。应采用合适的方法评估角质层的屏障完整性，以对上样用皮肤切片的有
C. Receptor Solution Qualification 接收介质确认
The composition and pH of the receptor solution used for the IVPT study should be qualified in relati
its compatibility with the skin as well as the stability and solubility of the drug in that receptor
solution. The stability of the drug in the receptor solution samples should be validated as part of t
receptor sample analytical method validation. The solubility of the drug in the IVPT receptor solutio
be empirically determined in triplicate, to illustrate that the solubility of the drug in the recepto
solution exceeds the highest sample concentration in the IVPT pivotal study, ideally by an order of
magnitude. The solubility of the drug in the IVPT receptor solution should be sufficient to characte
higher amounts of drug permeating from the increased drug delivery condition evaluated in the IVPT
sensitivity assessment during IVPT method validation.
IVPT研究中所用接收介质的组成和pH应根据其与皮肤的兼容性以及药物在接收介质中的稳定性和溶解度进行确认。
The inclusion of 0.1% polyoxyethylene[20]oleyl ether (also known as Oleth-20, Volpo-20, or Brij-20; C
number 9004-98-2) is recommended to enhance the solubility of physiological buffer based (aqueous) re
solutions for hydrophobic drugs. If additional solubility is needed, small increases in the concentra
polyoxyethylene[20]oleyl ether (e.g., from 0.1% or 0.2%, which is typically adequate for most hydrop
drugs, to higher concentrations) are recommended, but should not exceed 6% polyoxyethylene[20]oleyl e

Other strategies to improve the solubility of the drug in the receptor solution that may have the po
to alter the permeability of the skin (e.g., inclusion of organic solvents and alcohols in the recep
solution) are not recommended and may invalidate the IVPT method.
对于疏水性药物，推荐在基于生理缓冲盐的接收介质中添加0.1%(w/v)聚氧乙烯20油醚（别名Oleth-20, Volpo-20,
20；CAS：9004-98-
2）提高溶解度。如有必要，可在接收介质中略微增加聚氧乙烯20油醚的浓度[例如，从0.1%(w/v)到0.2%(w/v)]，通
The inclusion of an anti-microbial agent in the receptor solution (e.g., ~0.1% sodium azide or ~ 0.0
gentamicin sulfate) is recommended to mitigate potential bacterial decomposition of the dermis and/o
epidermis in the diffusion cell, regardless of the study duration. Other antimicrobial agents may al
acceptable, and if used, information should be included in the ANDA to explain the reason for their
(and for the concentration at which they were used).
无论研究时间的长短，建议在接收介质中加入一种抗微生物剂（例如，～0.1%叠氮化钠或～0.01%硫酸庆大霉素），
D. Receptor Solution Sampling Qualification 接收液取样确认
The accuracy and precision of receptor solution sample collection at each time point should be appr
qualified. Evidence to qualify a sampling procedure should illustrate that the sampling techn
reliably collect a consistent volume of the sample from the well-mixed volume of the receptor compa
each sampling event, and that no artifacts are likely to be created by the sampling technique. In
should be included describing the equipment manufacturer's specification for the accuracy and pre
receptor solution sampling, when available.
应对接收液中每个时间点取样的准确性和精密度进行适当的确认。在取样程序的确认过程中应证明，所用取样技术
?
For IVPT studies using a flow-through diffusion cell, it may be appropriate to qualify the lengths o
and their associated dead volumes, to accurately calculate the lag time before a sample elutes th
tubing and is collected. For IVPT studies using a VDC, removal of the entire receptor solution v
full volume replacement of the receptor solution at each time point may provide optimal solubi
conditions. The sampling of small aliquots of the receptor solution for an IVPT study may introduce
measurements of apparently negative flux in certain regions of the IVPT study and produce flux prof
are difficult to interpret.
对于采用流通扩散池进行IVPT研究的情况，应对流通扩散池每个管路的长度，以及相关的死体积进行确认，以准确
E. Environmental Control 环境控制
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
20% relative humidity is recommended, if feasible.
在研究期间，应监控和报告实验室环境的温度和湿度。如适用，建议将温度控制在21℃±2℃、湿度控制在50%RH±
F. Permeation Profile and Range 渗透曲线和范围
The flux profile and cumulative permeation profile for the IVPT pilot study should be plotted acros
of sampling times, which corresponds to the IVPT pivotal study duration. The calculation of
cumulative total permeation is discussed in more detail below. The results of the IVPT pilot stu
validate that the selected study parameters are suitable to adequately characterize the permeatio
(the cutaneous pharmacokinetics) of the drug within the selected study duration (the range of samp
points).
在IVPT初步研究和正式研究中，应在整个取样时间范围内分别绘制通量分布曲线和累积渗透分布曲线。下文有关于
A sufficiently complete flux profile should be adequate to identify the maximum (peak) flux and a d
the flux thereafter across multiple subsequent time points in the IVPT pilot study. The results of
pilot study should also validate that the sampling frequency provides suitable resolution to a

characterize the permeation profile (particularly the flux profile).
在IVPT初步研究中，一个充分完整的通量分布应足以识别出最大（峰值）通量和此后多个时间点的通量下降情况。
G. Precision and Reproducibility 精密度和重现性
The flux and cumulative permeation results from the IVPT pilot study (and the eventual IVPT pivot
should be calculated, tabulated, and reported for each diffusion cell at each time point, with
statistics to describe the intra-donor average, standard deviation, and percent coefficient of
(%CV) among replicates, as well as the inter-donor average, standard error, and %CV. Complete result
data values used in the calculations should be reported in a clear and organized manner, to facil
reconstruction of the flux and cumulative permeation results. The design of the study should be det
clear, and data values should be clearly associated with specific donors, replicates, treatment gro
points, etc.
在IVPT初步研究（和最终的IVPT正式研究）中，应计算和报告各扩散池在每个时间点的通量和累计渗透结果，并以
H. Dose Depletion 剂量消耗
The recovery of permeated drug in the receptor solution should be characterized in each diffusion ce
cumulative total permeation of the drug in the receptor solution over the IVPT duration. Thi
expressed as a percentage of the nominal amount of drug in the applied dose (which may be estima
upon the nominal strength of the drug in the topical product and the approximate mass of topica
dosed on the skin).
在IVPT研究期间，每个扩散池单元中药物渗透进入接收液中的回收率可以表征为“接收液中药物的总累积渗透量”
For example, if 10 mg of a topical product containing 5% drug was dosed on the membrane, the amoun
in the applied dose may be estimated to be 0.5 mg (or 500 μg). If a cumulative total of 10 μg
diffused into the receptor solution across a 48-hour duration of the IVPT, it would be possible to
that the 500 μg dose would have been depleted by approximately 10 μg, amounting to an approximatel
depletion. The average percentage dose depletion may thereby be estimated (not accounting for skin
and should be reported.
例如，如果含有5%
药物的外用制剂上样为10mg，则在上样中药物的量大约为0.5mg（或500μg）。如果在IVPT研究的整个48小时内，药
I. Discrimination Sensitivity and Selectivity 区分力—灵敏度和选择性
The discrimination ability of the IVPT method may be described using two concepts: sensiti
selectivity. The IVPT sensitivity studies are necessarily performed during IVPT method develo
establish IVPT method parameters like the dose amount, dose duration, study duration, etc. Howe
analysis of the results from these studies is qualitative in nature, and they need not be repeated d
IVPT method validation phase.
可以用以下两个概念描述IVPT方法的区分力：灵敏度和选择性。在IVPT方法开发期间，必须进行IVPT灵敏度研究，
The IVPT sensitivity studies are typically performed toward the end of the IVPT method development p
a key purpose of these studies is to incorporate the final IVPT method parameters for the target
dose duration to be used in the pivotal study so that the IVPT sensitivity studies can s
demonstration of the validity of the final IVPT method. Therefore, IVPT sensitivity studies are
within this section of the guidance in the context of IVPT validation (rather than method develo
avoid dissociating the discussions of IVPT sensitivity (which is performed to establish the suita
the final IVPT method parameters) and IVPT selectivity (which is performed once the final IVP
parameters are established, and which is based upon the IVPT pilot study that is performed as pa
IVPT method validation). With the exception of the alternative dose amounts or dose durations use
IVPT sensitivity study, it is important that the IVPT method parameters are consistent across
sensitivity, pilot, and pivotal studies (including the anatomical region specified in the study

(e.g., posterior torso), the skin source, and skin preparation).

IVPT灵敏度研究通常在IVPT方法开发阶段末进行，这些研究的一个关键目的是为了确定“在正式研究中所用的最终

1. IVPT Sensitivit 灵敏度

IVPT sensitivity is the ability of the IVPT method to detect changes in the cutaneous pharmacokineti drug as a function of differences in drug delivery. If the IVPT method consistently demonstrates h lower flux profiles (i.e., higher and lower values for IVPT endpoints) in response to increased and drug delivery, respectively (or in response to other conditions expected to increase and decre delivery, respectively), the IVPT method may be considered sensitive.

IVPT灵敏度是IVPT方法检测药物皮肤药代动力学变化的能力，以反映药物递送的差异。如果随着药物递送的增加和

There are a few potential approaches by which to produce the differences in drug delivery tha differentiated by a suitably discriminating IVPT method. Regardless of the approach used, the diffe the IVPT permeation profiles are not necessarily expected to be specifically proportional to diffe the dose amount, dose duration, or product strength. For example, three-fold differences in the do (even if outside the recommended target dose range) may provide distinct flux curves but may not three-fold differences in the IVPT endpoints because the skin barrier may be rate-limiting both in in vivo.

有几种潜在具有合适区分力的IVPT方法设计，去表征药物的不同递送行为。但无论采用何种方式，均不能期望IVPT

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

换言之，如果正式IVPT研究的目标剂量是10 mg/cm^2，则三倍的较低剂量为3 mg/cm^2，三倍的较高剂量为30 mg/ ；因此，可通过比较3、10和30 mg/cm^2

外用制剂上样量的通量曲线，确认IVPT方法的灵敏度。同理，如果正式IVPT研究的目标剂量是15 mg/cm^2 ，则三倍的较低剂量为5 mg/cm^2，三倍的较高剂量为45 mg/cm^2；因此，可通过比较5、15和45 mg/cm^2

外用制剂上样量的通量曲线，确认IVPT方法的灵敏度。在IVPT灵敏度研究中，建议采用多个皮肤供体（如，4～6个

- 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 appro well suited to topical products that contain volatile components that evaporate from the formulation following dose application to the skin. Modulating the dose amount for such topical products effecti alters the thickness of the applied dose. The majority of volatile components from a thinner dose wi to evaporate more rapidly (compared to a thicker dose), and a thinner dose will tend to deliver less into the skin (and/or for a shorter duration) compared to a thicker dose. 调整上样量 ：可以采用不同的上样量进行IVPT方法开发研究，为IVPT方法对药物递送的差异具有灵敏度提供支持性证据。

该方法适用于含有挥发性成分的外用制剂，这些挥发性成分在药物制剂上样到皮肤后会挥发。调整这类制剂的上样

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

对于含有挥发性组分的配方，如凝胶、洗剂和很多乳膏剂，调整上样量是改变药物递送行为的有效技术手段。然而

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

  调整剂量维持时间

  ：对于很多外用制剂，相比于调整上样量，通过调整剂量维持时间可更有效地评估药物递送的差异和与药物皮肤药

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

  在IVPT方法开发研究中，通过将一定量的外用制剂（如，15 mg/cm^2）在皮肤上维持不同的时间（如，2h、6h和12h）可能是提供支持性证据的比较合适方式，以证明IVPT方法对很多外 mg/cm^{2}的外用制剂在皮肤上维持6h（研究的目标维持时间），然后将其擦除。可以采用一些棉签移除样品，包括一个或多

  To support a demonstration of the sensitivity of the IVPT study, the permeation profile produced by target dose duration for the IVPT study (e.g., 6 hours) should be compared with a shorter dose durat (e.g., 2 hours) that is expected to perceptibly decrease the drug delivery, and also be compared wit longer dose duration (e.g., 12 hours) that is expected to perceptibly increase the drug delivery. Th the three dose durations compared in the IVPT sensitivity study are designed to produce perceptible in the cutaneous pharmacokinetics of the drug as a function of differences in drug delivery, and the support a demonstration of the sensitivity of the IVPT method.

  为了证明IVPT研究的灵敏度，将IVPT研究中目标剂量持续时间（如，6小时）的渗透曲线分别与较短剂量维持时间

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

  在IVPT方法开发期间，可以根据初始的探索性IVPT研究中，剂量在皮肤上保留较长时间（如，24或48小时）的渗透

  For example, if such an exploratory study indicates that the flux increases on a steep slope until approximately 12 hours, and then continues to deliver the drug at a gradually increasing rate therea may suggest that the permeation profile for a dose duration of longer than 12 hours (e.g., 24 hours) be perceptibly different from that of the 12 hour dose duration, especially when compared in a relat small number of donors and replicates (e.g., four donors with four replicates each per dose duration also suggest that a 12-hour dose duration may be a good choice for the longest of the three dose dura the IVPT sensitivity study.

  例如，如果探索性研究结果表明，在12小时前通量快速增加，之后随着剂量维持时间的增加，通量与12小时无明显

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

  目标剂量维持时间的选择应基于以下考虑因素，如：样品分析方法的灵敏度、产生能明显区别于最长（12小时）剂

The shortest of the three dose durations in the IVPT sensitivity study should be selected based upon sensitivity of the sample analytical method and its ability to produce a permeation profile that can perceptibly discriminated from that produced by the target (6 hour) dose duration.
在IVPT灵敏度研究中，三个剂量维持时间中最短时间的选择应基于样品分析方法的灵敏度，以及其产生能明显区别

- Modulation of Product Strength: To validate the sensitivity, specificity, and selectivity of an in v release test (IVRT) method, altered strength formulations are routinely prepared. While it may seem convenient to use these altered strength formulations in an attempt to demonstrate the sensitivity a selectivity of an IVPT method, doing so may not produce the desired outcomes. There may be circumsta this strategy may produce perceptibly different permeation profiles, however, in many instances, the resulting permeation profiles may not be perceptibly different when compared in a relatively small nu donors and replicates (e.g., four donors with four replicates each per topical product strength). In the modulation of topical product strength to support a demonstration of IVPT sensitivity is not rec because it may not consistently produce the expected increase or decrease in drug delivery; however, certain situations, higher and lower strength formulations (relative to the nominal strength of the suitably increase and decrease the drug delivery and cutaneous pharmacokinetics relative to that fro nominal strength topical product.
调整产品规格
：对于IVRT方法的灵敏度、专属性和选择性验证而言，常见的方式是改变配方制剂的规格。虽然在IVPT方法的灵敏

2. IVPT Selectivity 选择性IVPT selectivity is the ability of the IVPT method to discriminate the cut pharmacokinetics of the drug between the RS and a topical product or formulation that exhibits diffe drug delivery relative to the RS. The IVPT pilot study with the parallel assessment of the RS, the t topical product, and a third topical product or formulation that is known or designed to be differen the RS may provide supportive evidence that the IVPT methodology is selective for differences in dru delivery. Topical product batch information for all topical product lots used in IVPT method develop validation and pilot studies, as applicable, should be submitted in the study reports. The topical p information should include, but not be limited to, information about the batch formula, manufacturin batch size, altered manufacturing processes (if applicable) and, if available, potency and content uniformity. The evaluation of inequivalence may be based upon a qualitative or quantitative compari permeation profiles and/or the IVPT endpoints.
IVPT选择性是IVPT方法区分“对照制剂（RS）”和“与RS在药物递送方面存在差异的外用制剂或配方”在药物皮肤

J. Robustness 耐用性
A primary assumption related to robustness testing is that the test system performs consistently system variables (e.g., temperature, stirring rate) are at nominal settings. A value of robustness t that it can verify whether the system continues to provide a consistent output when specific vari slightly altered, thereby qualifying operational ranges for those variables. However, the va inherent in the permeability of human skin, whether in vitro or in vivo, may not be compatible primary assumption related to the consistency of the test system.
与耐用性测试相关的一个主要假设是，当所有系统变量（如，温度、搅拌速率）为标准设置时，测试系统的性能一
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 substantial variations in the stirring rate of the receptor compartment. Similarly, the permeation p a drug into and through human skin may appear to be robust to certain differences in the topica strength. Ultimately, because it may not always be feasible to validate the robustness of IV parameters, IVPT study procedures should be controlled as precisely as possible.

尽管如此，如果相关，应报告在IVPT方法开发期间获得的可以支持IVPT方法或系统耐用性的研究结果。例如，IVPT

V. Sample analytical method validation 样品分析方法验证

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 valida sample analytical method. A validated IVPT method should use a validated sample analytical method (e. HPLC/MS or UPLC/MS). Therefore, a discussion of the sample analytical method for the IVPT method is in this guidance under this section on IVPT method validation.

虽然在IVPT方法开发的探索性研究中，可以采用未验证的样品分析方法，但作为IVPT方法验证的一部分，在IVPT方

However, the study protocols 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. The validation of a sample analytical method, in and of itself, does not demonstrate the validity of an I method. Separate and specific reports should be submitted for the validation of the sample analytical (e.g., HPLC/MS or UPLC/MS) and for the validation of the IVPT method.

然而，与IVPT方法相关的研究方案和报告与用于IVPT接收液中样品定量的分析方法不同。样品分析方法验证，就其

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

如果，在方法开发期间使用的样品分析方法与最终验证的样品分析方法不同，与其相关的IVPT方法研究结果不能用

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

接收液中样品的分析方法（如，通常为HPLC/MS或UPLC/MS系统）应使用具有审计追踪的色谱软件（如，色谱数据系

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

如适用，接收液中样品分析方法的验证应包括相关的稀释完整性确认，以及样品在最高相关温度的接收液中放置最

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

如果在测定前，需要用特定的方式对样品进行处理（如：将样品干燥后重新用小体积溶剂配制以提高分析灵敏度；

VI. IVPT Pivotal study IVPT正式研究

The IVPT pivotal study protocol should incorporate consideratio relevant to BE studies, in general. IVPT正式研究方案通常应包含与BE研究相关的考虑因素。A. Handling and

Retention of Samples 样品的处理和保存

Refer to 21 CFR 320.38, 320.63 and the FDA guidances for industry Handling and Retention of BA and B Samples (May 2004) and Compliance Policy for the Quantity of Bioavailability and Bioequivalence Retained Under 21 CFR 320.38(c) (August 2020), as applicable, regarding considerations for retention drug samples and to 21 CFR 320.36 for requirements for maintenance of records of BE testing. samples should be randomly selected from the drug supplies received before allocating topical prod for use in an IVPT study in which the test topical product and RS are compared.

参考21 CFR 320.38，320.63和FDA行业指南《生物利用度（BA）和生物等效性（BE）研究中试验样品的处理和保存》（2004年5 320.38(c) BE样品留存的数量及生物利用度》（2020年8月），如适用，关于保留研究药物样品的考虑以及21 CFR 320.36关于保存BE检测记录的要求。在采用自研外用制剂和RS进行IVPT对比研究前，应从收到的药品中随机选择样

B. Control of Study Procedures 研究程序的控制

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

应对可能影响研究结果的研究程序进行适当控制。另外，应报告可能影响研究结果解释的试验观察，以及任何与方

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

与皮肤相关的控制程序，包括：采用相同的皮肤处理方法（如，皮肤的剥离）和安装在扩散池上皮肤切片的厚度的

Control of procedures related to the dose include the control of the area of dose application, the d amount, the dosing technique, the dose duration, and the blinding and randomization consistent manne diffusion cells in the study. Differences in dosing technique may alter the metamorphosis of the dosa on the skin, and inconsistencies in the diameter of the area dosed on each diffusion cell may signif influence the dosed area and contribute to errors in the calculation of flux.

与剂量或上样相关的控制程序，包括：对上样面积、上样量、上样技术、剂量维持时间的控制，以及在研究中每个

Control of procedures related to sampling include the control of sampling time precision, the samplin technique, the duration of sampling and replacement of receptor solution, the sample volume or flow sample handling and storage.

与取样相关的控制程序，包括：取样时间精准度、取样技术、取样和替代接收液的时间间隔、取样体积或流速，以

Control of procedures related to the pivotal study should include a non-dosed control skin section f skin donor, which should be mounted in a diffusion cell and otherwise treated identically to the dose sections, including sampling of the receptor solution at all time points to ensure that drug concentr monitored in the receptor solution are associated with the dose applied in the IVPT pivotal study, a drug contamination in the skin from that donor that might permeate into the receptor solution across

duration of the study. A pre-dose "zero" sample collected from each diffusion cell is also recomme
which may identify potential contamination associated with each skin section and/or each diffusion c
在正式研究期间的相关控制程序，包括：对每组皮肤供体的非剂量控制皮肤切片，按照与上样皮肤切片一致的方式
In addition, investigators should perform the IVPT validation and pivotal studies within a quality ma
system that includes, but is not limited to, documented procedures for:
此外，研究人员应在一定的质量管理体系条件下，进行IVPT验证和正式研究，包括但不限于：

- Study personnel identification, training, qualification, and responsibilities
  研究人员的识别、培训、资质和职责
- Study management and study management personnel responsibilities 研究管理和研究管理人员职责
- Quality control (QC) and QC personnel responsibilities 质量控制（QC）和QC人员职责
- Quality assurance (QA) and QA personnel responsibilities 质量保证（QA）和QA人员职责
- Use of SOPs 操作规程（SOP）的制定
- Use of study protocols 研究方案的制定
- Use of study reports 研究报告的制定
- Maintenance and control of the study facility environment and systems 研究设施环境和系统的维护和控制
- Qualification and calibration of instruments and computerized systems 仪器和计算机系统的确认和校准
- Good documentation practices including, but not limited to, contemporaneous documentation of study p
  and recording of experimental observations or deviations from procedures specified in the study proto
  in relevant SOPs
  良好的文件规范，包括但不限于：及时记录研究过程、试验观察、以及与研究方案及相关SOPs中规格程序的偏离
- Maintenance of suitable records that facilitate the reconstruction of study events and procedures, i
  study sample handling and storage records (e.g., sample tracking logs), audit trails for sample analy
  procedures, control of study materials and reagents, and electronic data control
  对记录进行适当的维护，以便研究过程可以重现，包括：研究样品的处理和保存记录（如，样品跟踪日志）、样品
  Archival of study records 研究记录归档

C. Blinding Procedure 盲法程序

A detailed description of the blinding procedure should be provided in the study protocol and fina
The packaging of the test topical product and RS should be similar in appearance to maintain
blinding of the investigator and any experimental operators.
应在研究方案和最终报告中递交详细的盲法程序信息。自研外用制剂和RS的包装应有相似的外观，以确保对研究人

D. Randomization 随机化

The method of randomization should be described in the protocol of the IVPT study and the rand
schedule provided, preferably in a SAS data set in .xpt format (created using the SAS XPORT procedur
recommended that an independent third party generate and hold the randomization code throughout th
of the study to minimize bias. The applicant may generate the randomization code if not involve
packaging and labeling of the test topical product and RS dosed in the study. A sealed cop
randomization scheme should be retained at the study site and should be available to FDA investigato
time of site inspection to allow for verification of the treatment identity of each skin section.
应在IVPT研究方案中描述随机化方法，并推荐以.xpt格式的SAS数据集形式（使用SAS
XPORT程序创建）提供随机化计划表。在整个研究过程中，建议由独立的第三方生成并保存随机化代码，以减少偏差

E. Dosing 上样

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

a. ABABAB…

b. BABABA…

在IVPT正式研究中，对于每个供体组，可以在扩散池（皮肤切片）上以交替给药方式依次放置自研外用制剂和RS。

a. ABABAB…

b. BABABA…

F. Study Design 研究设计

The IVPT pivotal study should compare the cutaneous pharmacokinetics of the drug from the test product versus that from the RS using excised human skin with a competent skin barrier mounted on a diffusion cell system. The IVPT pivotal study should use a design that directly compares the test product and RS on skin from the same set of donors, each with the same number of replicate skin sec donor per treatment group (dosed with either test topical product or RS topical), using the same IV parameters.

在IVPT正式研究中，应采用皮肤屏障完整性良好的离体人类皮肤和经确认的扩散池系统，对自研外用制剂和RS的皮

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 st dose application on successive diffusion cells and to synchronize the sampling time points with t time for that diffusion cell, to ensure consistent durations between dosing and sampling of all cells.

应尽可能精准的控制IVPT正式研究的设计、方法和扩散池设备的取样精密度。例如，对于连续的扩散池，可以错开

G. Inclusion Criteria 纳入标准

In general, the following inclusion criteria should apply: healthy, normal, barrier-competent skin and/or female donors of at least 18 years of age. Inclusion criteria related to donor demographi age, race, sex) should be specified in the study protocol and demographic information should be rep each donor. Additional criteria may be added by the applicant.

通常，应采用以下纳入标准：至少18周岁的健康、正常、具有屏障完整性的雄性和/或雌性供体。应在研究方案中规

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

建议使用人体离体皮肤，可以从接受外科手术的病人或尸体获取。所用的所有皮肤应有一致的来源，且所有的供体

The study protocol should specify the inclusion (acceptance) criteria for skin sections based barrier integrity test result, which should be reported for each skin section. The study protoco specify inclusion criteria related to the temperature and duration of skin storage as well as the freeze-thaw cycles, all of which should be reported for each donor’s skin. The study protocol shoul the inclusion criteria related to the skin harvesting/processing procedures and skin thickne dermatomed skin of 500 μm ± 250 μm thickness) used in the IVPT study.

研究方案中应规定皮肤切片的屏障完整性测试纳入（接受）标准；并规定每组供体皮肤的储存温度和时间，以及冻 μm ± 250 μm）。

H. Exclusion Criteria 排除标准

In general, the following exclusion criteria should apply. Skin from subjects with a known (his dermatological disease should be excluded from the study. Skin with tattoos, stretch marks, or an sign of abnormality should be excluded from the study. Skin exhibiting a significant density of term is not recommended and should be excluded from the study. Additional criteria may be added by the ap

通常，应采用以下排除标准。包括：患有已知皮肤疾病（病史）的供体皮肤；带有纹身、妊娠纹或任何异常迹象的

While gentle washing or rinsing of the skin surface is appropriate, submerging the skin in ar solution for more than a few minutes may damage the skin barrier and should be avoided; such skin should be excluded from the study. Also, skin that has been subjected to shaving with a blade; polishing; tape-stripping; or cleansing with alcohols, solvents, or other strong solutions that cou the skin barrier should be excluded from the study.

虽然可以采用温和的清洗或冲洗方式处理皮肤表面，但是，如果将皮肤浸泡在水溶液中几分钟，就有可能破坏皮肤

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

含有显著的药物背景水平或含有的其他化合物可能干扰接收液中药物定量测定的皮肤供体，应排除在研究之外。重

I. IVPT Endpoints IVPT终点

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

IVPT关键研究的皮肤药代动力学终点是基于表征药物渗透和通过皮肤进入接收液的速率和程度的参数。具体来说，

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

以通量（药物渗透速率）为纵坐标Y-轴，时间为横坐标X-轴作图；其中Y-

轴用“J”标识，以质量/面积/时间（如，纳克/平方厘米/小时）为单位。通量分布模型通常类似于血浆药代动力学

轴，时间为横坐标X-轴。

The flux should be calculated based upon: the receptor sample concentration (e.g., 2.0 ng/mL) at each point; the precise, empirically measured volume of that specific diffusion cell (e.g., 6.0 mL) which between individual cells; the area of dose application (e.g., 1 cm^2); and the duration for which the volume was accepting the drug. For example, if the sample exemplified here represented a 2-hour perio following dosing, then J would be calculated based upon the values above as:

通量的计算应基于：每个时间点的接收液中样品的浓度（如，2.0 ng/mL）；精确的、经验测量的扩散池的体积（如 mL），每个扩散池的体积可能不同；上样区域的面积（如，1 cm^2

）；和整个研究的持续时间。例如，如果此处所示样本代表给药后2小时内的情况，则J值按下式进行计算：J = [(ng/mL) x (6.0 mL)]/(1 cm^2)/(2 hrs) = 6 ng/cm^2/hrThis flux should be calculated and reported for each diffusion cell for each sampling interval and plotted across the entire study duration to generate th profile for each diffusion cell. The rate calculated above may be plotted at the 2-hour time point, midpoint between 0 and 2 hours (i.e., 1 hour).In addition, the AMT should be calculated and reported diffusion cell. This cumulative amount of drug that has permeated (in total across the entire study) be reported as the AMT endpoint, rather than using a trapezoid rule to calculate the area under the curve.

应计算并报告各扩散池的所有相邻采样点之间的通量，并为整个研究期间的所有扩散池绘制通量曲线。上述计算的

此外，应计算并报告每个扩散池的总累计渗透量（AMT）。AMT终点为药物渗透的累计量（整个研究期间的渗透总量

The maximum flux (Jmax) at the peak of the drug flux profile and the AMT should both be compared for acting test topical products and RSs. This is somewhat analogous to the comparison of the Cmax and AU

systemically-acting test products and RSs, inasmuch as the pair of endpoints in each case facilitates comparison of the rate and extent to which the drug from each type of product (locally-acting or systemically-acting) becomes available at the site of action.A confidence interval (CI) should be ca for each IVPT endpoint: a. the natural log-transformed maximum flux (Jmax) b. the natural transformed total cumulative amount (AMT) permeated

应将局部起效的自研制剂和RSs的最大通量（Jmax，药物通量曲线的最高峰）和AMT进行对比。这类似于全身起效的

a. 自然对数换算后的最大通量（Jmax）

b. 自然对数换算后的总累积渗透量（AUC）

It is the responsibility of the applicant to determine the number of donors required to adequately IVPT pivotal study, however, a minimum of four dosed replicates per donor per treatment group (tes or RS) is recommended.

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

申请人有责任确定足以支持IVPT关键研究所需的供体数量，然而，建议每个试验组（自研制剂或RS）每个供体至少

在IVPT研究结束时，如果自研外用制剂和RS试验组中所有供体的皮肤切片重复数均一致，建议采用平衡设计法进行

Approaches to statistical analysis of the pivotal study are described in section VIII of this guidan Appendix I provides example SAS code for determining BE with both a balanced dataset and an unbalanc dataset. Appendix II provides numerical examples with simulated data sets. Appendix III provides exa code for determining BE.

在本指南的第VIII部分，对正式研究的统计分析方法进行了描述。附录I提供了用于测定平衡数据集和非平衡数据集

VII. Submitting information on IVPT studie ANDA中递交的IVPT研究信息

For IVPT studies with topical products submitted in ANDAs that are intended to support a demonstrati detailed study protocols, relevant SOPs, and detailed reports should be submitted for the IVPT metho validation (including the IVPT pilot study) and the IVPT pivotal study. In addition, a detailed repo describing the IVPT method development should be submitted. These protocols, SOPs, and reports shoul submitted in module 5.3.1.2 of the electronic Common Technical Document (eCTD) and should describe experimental procedures, study controls, quality management procedures, and data analyses.

对于支持外用制剂产品BE论证的IVPT研究，在ANDA申请中应递交IVPT方法验证（包括IVPT初步研究）和IVPT正式研

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

注意：用于IVPT接收液中样品浓度的定量分析方法（如，HPLC/MS或UPLC/MS方法）与IVPT方法相关的研究方案、SO