**<1724> 半固体药品性能试验**

<1724> SEMISOLID DRUG PRODUCTS—PERFORMANCE TESTS

**范围**

SCOPE

This chapter provides general information about developing in vitro performance tests to evaluate drug release or skin permeation for topical and transdermal semisolid and liquid-based dosage forms, including but not limited to, creams, gels, ointments, pastes, suspensions, lotions, and foams. For information related to in vitro performance tests that evaluate drug release for transdermal delivery systems (TDS), refer to Drug Release <724>.

本章提供了用于评价局部和透皮半固体和液体剂型的药物释放或皮肤渗透的体外性能试验的一般信息，剂型包括但不限于面霜、凝胶、软膏、膏剂、悬浮液、乳液和泡沫。有关评估透皮给药系统(TDS)药物释放的体外性能试验的相关信息，请参阅药物释放<724>。

In this chapter, the term “drug” is utilized to refer more generally to active ingredients, potentially including active ingredients that may not be considered drugs (e.g., sunscreen active ingredients).

在本章中，“药物”一词更一般地指活性成分，可能包括不被视为药物的活性成分(如防晒霜活性成分)。

For information related to product quality tests for topical and transdermal dosage forms, refer to Topical and Transdermal Drug Products—Product Quality Tests .

有关外用和透皮剂型产品质量测试的相关信息，请参阅外用和透皮药品-产品质量测试。

**引言**

INTRODUCTION

This chapter provides general information for developing in vitro release test (IVRT) methods to assess the rate of drug release from topical and transdermal semisolid and liquid-based dosage forms, including but not limited to, creams, gels, ointments, pastes, suspensions, lotions, and foams applied on the skin and other mucosal membranes. Definitions and descriptions of these dosage forms can be found in Pharmaceutical Dosage Forms <1151>. This chapter also provides general information for developing in vitro permeation tests (IVPT) to assess the rate and extent of drug permeation into and through the skin from semisolid and liquid-based drug products. The same equipment and similar methodological principles/procedures may be relevant for IVPT methods with other epithelial membranes (for information on appropriate mucosal membranes, see Biological Membrane below).

本章提供了开发体外释放试验(IVRT)方法的一般信息，以评估药物从外用和透皮半固体和液体剂型的释放速度，包括但不限于药膏、凝胶、软膏、膏体、悬浮液、乳液和涂抹在皮肤和其他粘膜上的泡沫。这些剂型的定义和描述可在药物剂型<1151>中找到。本章还提供了开发体外渗透试验(IVPT)的一般信息，以评估药物从半固体和液体药物制品渗透到皮肤和通过皮肤的速度和程度。相同的设备和类似的方法原则/程序可能与其他上皮膜的IVPT方法相关(有关合适粘膜的信息，请参见下文的生物膜)。

**药品质量和性能测试**

Drug Product Quality and Performance Tests

Drug product tests are divided into two categories: 1) those that assess general quality attributes i.e., product quality tests, and 2) those that assess product performance, e.g., using an IVRT/IVPT method. Product quality tests characterize the physicochemical and/or structural attributes (e.g., pH, particle size/morphology etc.) of the formulation. By contrast, product performance tests assess how a drug product functions under specified conditions, which may provide information relevant to its in vivo performance.

药品检验分为两类:1)评估一般质量属性的试验，即产品质量检验;2)评估产品性能的试验，如使用IVRT/IVPT方法。产品质量测试表征配方的物理化学和/或结构属性(例如，pH值、粒度/形态等)。相比之下，产品性能测试评估药物产品在规定条件下的功能，这可能提供与其体内性能相关的信息。

Product quality tests are generally useful to characterize and/or compare product quality attributes that can control the performance of the product, including, but not limited to, identity, strength, purity, uniformity, pH, particle size/morphology, and apparent viscosity. Details about these product quality tests can be found in á3ñ. The performance tests that are the focus of this general chapter are specifically useful to characterize and/or compare the linear (steady state) drug release rate (using an IVRT) or the dynamic rate and extent to which a drug permeates into and through the skin (using an IVPT) from semisolid and/or liquid-based dosage forms, under the conditions of the test.

产品质量测试通常可用于表征和/或比较可控制产品性能的产品质量属性，包括但不限于特性、强度、纯度、均匀性、pH值、粒度/形态和表观粘度。有关这些产品质量测试的详细信息可在<3>中找到。本通则重点介绍的性能测试，在测试条件下，对于表征和/或比较线性(稳态)药物释放率(使用IVRT)或药物从半固体和/或液体剂型渗透到皮肤和通过皮肤的动态速率和程度(使用IVPT)特别有用。

Potential contexts for use of IVRT and IVPT methods are summarized below.

**以下概述了使用IVPT和IVRT方法的潜在环境：**

• Characterizes the steady-state drug release rate for a product batch. When the performance (release rate) of a topical product has been characterized by a validated IVRT method using the same batch of product that supported a demonstration of the safety and/or efficacy of the product, that performance (release rate) may have the potential to serve as a basis of reference for the product in the future

**· 表征一个产品批次的稳态药物释放速率。当外用产品的性能(释放率)通过验证的IVRT方法进行表征时，使用支持产品安全性（和/或）有效性证明的同一批产品，该性能(释放率)可能有潜力作为将来产品的参考基础**

• Characterizes the influence of processes, formulations, and/or manufacturing differences on a drug product by comparing the steady-state drug release rate for the postchange (test) and prechange (reference) products, typically in the context of scale-up or post–approval changes for an approved drug product, which can support a demonstration of equivalence in certain situations

**· 通过比较变更后(试验)和变更前(参考)产品的稳态药物释放率来表征工艺、配方和/或制造差异对药品的影响，通常在已批准药品的放大或批准后变更的背景下，这可以支持在某些情况下证明等效性**

• Characterizes the influence of processes, formulations, and/or manufacturing differences on a drug product by comparing the steady-state drug release rate for a prospective generic (test) product and an approved (reference standard) product, which can support a demonstration of bioequivalence in certain situations

**· 通过比较预期仿制(试验)产品和批准(参考标准)产品的稳态药物释放率，表征工艺、配方和/或生产差异对药品的影响，这可以在某些情况下支持生物等效性的论证**

• Characterizes the rate and extent to which a drug permeates into and through the skin for a product batch

**· 描述一个批次产品中药物通过皮肤渗透的速率和程度**

• Characterizes the influence of process, formulation, and/or manufacturing differences on a drug product by comparing the rate and extent to which a drug permeates into and through the skin. This may occur in the context of comparing prototype formulations of a topical product, or potentially in the context of comparing postchange (test) and prechange (reference) products

**· 通过比较药物渗入和通过皮肤的速度和程度来表征工艺、配方和/或制造差异对药品的影响。这可能发生在比较局部产品的原型配方的情况下，或者可能发生在比较变更后(测试)和变更前(参考)产品的情况下**

• Characterizes the influence of process, formulation, and/or manufacturing differences on a drug product by comparing the rate and extent to which a drug permeates into and through the skin for a prospective generic (test) product and an approved (reference standard) product, which can support a demonstration of bioequivalence in certain situations

**· 通过比较药物进入和通过皮肤的速度和程度来表征工艺、配方和/或生产差异对药品的影响，这可以支持在某些情况下生物等效性的论证**

An IVRT is intended to characterize a steady-state drug release rate from a semisolid formulation under a specific set of conditions (i.e., a given set of method parameters). IVRT methods are typically precise and reproducible. However, if the parameters of the IVRT method change, then the release rate measured may also change. Notably, when the IVRT method is consistent, then changes in the release rate between a test and reference formulation are reflective of a difference in the physicochemical properties and/or the structural arrangement of matter in the formulations. Thus, IVRT methods can provide a sensitive and discriminating way to monitor for differences in the physicochemical or structural properties of a test versus the reference formulation.

IVRT旨在表征在一组特定条件下半固体制剂的稳态药物释放率(即，一组给定的方法参数)。IVRT方法通常是精确和可重复的。然而，如果IVRT方法的参数发生变化，则测量的释放率也可能发生变化。值得注意的是，当IVRT方法一致时，测试制剂和参比制剂之间释放速率的变化反映了制剂中物质的物理化学性质和/或结构排列的差异。因此，IVRT方法可以提供一种敏感和鉴别的方法来监测测试物与参考制剂的物理化学或结构特性的差异。

The steady-state drug release kinetics are not representative of the finite dose (non-steady-state) kinetics of drug permeation through the skin. The drug release rate measured by an IVRT method should not be misconstrued to represent a “true” drug release rate for that formulation, or even a biorelevant release rate. For these reasons, IVRT methods are most appropriate to assess (compare) the "sameness" of formulations (e.g., before and after certain manufacturing or formulation changes).

稳态药物释放动力学不能代表药物通过皮肤的有限剂量(非稳态)动力学。通过IVRT方法测量的药物释放率不应被误解为代表该制剂的“真实”药物释放率，甚至是生物相关释放率。由于这些原因，IVRT方法最适合评估(比较)配方的“一致性”(例如，在某些生产或配方更改之前和之后)。

If the drug release rate is found to be different between a test and reference formulation of comparable components and composition, it typically indicates that there is a difference in the physicochemical and/or structural attributes between the formulations. The IVRT methods discussed in this chapter are not expected to predict whether an observed difference in measured release rate may impact in vivo bioavailability, nor can they identify the exact nature of the difference. Instead, the utility of IVRT studies is that they can efficiently assess whether test and reference products perform in a manner that appears to be the same. When the drug release rates are equivalent for two formulations with similar components and compositions, it suggests that there may be a high degree of sameness in physicochemical and structural attributes between the formulations, thereby providing evidence that mitigates the risk of a potential difference in therapeutic performance. Consequently, IVRT studies may provide evidence to support a demonstration of equivalence between prechange and postchange batches of a product, or to support a demonstration of bioequivalence in certain situations.

如果发现药物释放率在可比较成分和组合物的试验制剂和参比制剂之间存在差异，则通常表明制剂之间在物理化学和/或结构属性上存在差异。本章讨论的IVRT方法并不能预测所观察到的释放率差异是否会影响体内生物利用度，也不能确定差异的确切性质。相反，IVRT研究的效用在于，它们可以有效地评估测试产品和参考产品是否以似乎相同的方式执行。当两种成分和成分相似的制剂的药物释放率相等时，这表明制剂之间在物理化学和结构属性上可能存在高度的相似性，从而提供证据，减轻治疗效果潜在差异的风险。因此，IVRT研究可以提供证据来支持产品更改前批次和更改后批次之间的等效性论证，或支持在某些情况下的生物等效性论证。

After a short lag period, release of drug from the semisolid dosage form is kinetically described by diffusion of a chemical out of a semi-infinite medium into a sink, by the following equation:

**在短暂的滞后期后，药物从半固体剂型中释放的动力学描述为化学物质从半无限介质中扩散到漏槽中，公式如下:**

Where m is the amount of drug released, Q is total amount of the drug in solution and suspended in the matrix, Dm is the drug diffusion coefficient in the semisolid matrix, Cs is the drug solubility, and t is time.

**式中m为药物释放量，Q为药物在溶液中和悬浮在基质中的总量，Dm为药物在半固体基质中的扩散系数，Cs为药物溶解度，t为时间。**

A plot of m versus √t will be linear with a slope of:

**m对√t的曲线是线性的，斜率为：**

IVRT method development should encompass key aspects that influence the IVRT results, including the IVRT receptor solution sample analysis method. IVRT method validation is outside of the scope of this chapter. An IVRT method transfer between laboratories should include a demonstration that the IVRT method and the associated IVRT receptor solution sample analysis method produces comparable, valid results when compared between the laboratory where the methods were validated and the laboratory to which the methods are transferred.

IVRT方法的开发应包括影响IVRT结果的关键方面，包括IVRT受体溶液样本分析方法。IVRT方法验证不在本章的讨论范围之内。实验室之间的IVRT方法转移应包括证明IVRT方法和相关的IVRT受体溶液样品分析方法在方法验证的实验室和方法转移到的实验室之间进行比较时产生可比的、有效的结果。

Filter membranes (e.g., 0.45-µm pore size) comprised of synthetic materials (e.g., mixed cellulose esters, nylon, polysulfone, polyethersulfone) are frequently suitable for IVRT methods as they are typically resistant to binding most drugs, and they permit drugs to diffuse through the membrane. Filter membranes comprised of a synthetic material, sometimes with different pore sizes, are commonly evaluated during IVRT method development. Other types of simple, monolayer synthetic membranes, like dialysis membranes, may also be suitable for an IVRT method. The use of biological membranes or synthetic membranes developed to emulate a biological membrane are not appropriate for an IVRT method because such membranes may inappropriately influence the apparent rate of drug release.

由合成材料(例如，混合纤维素酯、尼龙、聚砜、聚醚砜)组成的过滤膜(例如，孔径为0.45-µm)通常适合于IVRT方法，因为它们通常对大多数药物具有低吸附性，并且它们允许药物通过膜扩散。由合成材料组成的过滤膜，有时具有不同的孔径，通常在IVRT方法开发期间进行评估。其他类型的简单的单层合成膜，如透析膜，也可能适用于IVRT方法。使用生物膜或模拟生物膜的合成膜不适合IVRT方法，因为这种膜可能不恰当地影响药物的表观释放速度。

Suitable equipment for the IVRT method includes various models of vertical diffusion cell (VDC) and immersion cells. The most commonly used equipment for IVRT methods are VDC (see Figures 1–5), although immersion cells (Figure 6 and Figure 7) also have been used successfully. Equipment features (e.g., bubble-free cells or cells with a vent hole) other than the ones depicted below may be suitable once qualified. The total receptor compartment volume of VDC typically ranges from 5–15 mL, while the total vessel volume for the immersion cell typically varies between 50 and 200 mL; values outside of those typical ranges may be available depending on the manufacturer of the equipment. VDCs may offer advantages over immersion cells; for example, in the assessment of lower strength dosage forms and/or dosage forms with low amounts of drug release, VDCs provide less drug dilution in the receptor solution, minimizing potential analytical challenges regarding drug quantification. Also, many VDC models allow the user to adjust the amount of the dosage form utilized, which can allow users to increase the amount of the dosage form in the donor compartment, thereby reducing the percent dose depletion and sustaining the pseudo-infinite dose conditions that support steady-state drug release kinetics. See Equipment for further details on the equipment used in IVRT.

适用于IVRT方法的设备包括各种型号的垂直扩散池(VDC)和浸没池。尽管浸没池(图6和图7)也被成功应用，IVRT方法最常用的设备是VDC(见图1-5)。除了下面描述的设备特征(例如，无气泡池体或带有排气孔的池体)，一旦合格，可能也适用。VDC的总受体室容积通常在5 - 15ml之间，而浸没池的总容器容积通常在50 - 200ml之间;根据设备制造商的不同，可能会有超出这些典型范围的值。VDC可能比浸没池更有优势;例如，在评估低强度剂型和/或药物释放量低的剂型时，VDC在受体溶液中提供较少的药物稀释，最大限度地减少了药物定量方面的潜在分析挑战。此外，许多VDC模型允许用户调整所用剂型的量，这可以允许用户增加供体室中剂型的量，从而减少剂量消耗的百分比并维持支持稳态药物释放动力学的准无限剂量条件。有关IVRT中使用的设备的详细信息，请参阅设备。

The analytical method should be precise, accurate, and specific for the drug in the receptor solution. The use of validated analytical methods with multipoint calibration curves is encouraged. The validation of an analytical method for IVRT sample analysis is done separately from the validation of an IVRT method, which follows specific procedures not described in this chapter.

**分析方法对受体溶液中的药物应是精确、准确和特异性的。鼓励使用经过验证的多点校准曲线分析方法。IVRT样品分析的分析方法的验证与IVRT方法的验证是分开进行的，其遵循本章未描述的特定程序。**

**试验设计**

Experimental Design

When utilizing an appropriately selected receptor solution, membrane, equipment, dose, and sampling duration (as well as other potential method parameters) the release rate of the drug should be linear (when plotted as the amount of drug released versus the square root of time) and reproducible. The amount of drug product in the donor compartment should ensure that dose depletion does not occur to an extent that alters the linear (steady state) release kinetics during the duration of the test (i.e., a pseudo-infinite dose amount should be utilized). Excessive dose depletion is characterized by a nonlinear region in the plotted cumulative amount of drug released curve (when plotted as the amount of drug released versus the square root of time).

当使用适当选择的受体溶液、膜、设备、剂量和取样时间(以及其他潜在的方法参数)时，药物的释放速度应该是线性的(当绘制为药物释放量与时间的平方根时)并且可重复。给药室中的药物用量应确保在试验过程中，剂量消耗不会达到改变线性(稳态)释放动力学的程度(即，应使用伪无限剂量)。过量剂量消耗的特征是在绘制的药物累积释放量曲线中出现一个非线性区域(当绘制为药物释放量与时间的平方根时)。

The dose application can be done by different methods, such as, but not limited to, dispensing directly on the membrane from a tube, transferring and spreading on the membrane with a spatula, or transferring and dispensing with a positive-displacement pipette or a disposable harvester (which minimizes shear stress during dosing). The shear stress imposed upon the dosage form during the dispensing (e.g., from a product tube) and dosing (e.g., using a positive displacement pipette) should be considered, and the dosing method should preferably minimize and routinely control the shear stress in a consistent manner for all diffusion cells. It is also important that a consistent amount of the dosage form is applied uniformly upon the membrane, without air pockets, making a compact cylinder of the formulation. The diffusional surface area of the product on the membrane needs to be consistent and well controlled as it is a factor in the calculation of the release rate. The donor compartment should be occluded to avoid evaporation of volatile components (including water) from the dosage form that is in contact with the membrane, because that evaporative metamorphosis may lead to changes in the composition of the drug product and may alter its linear (steady state) drug release kinetics.

上样可以通过不同的方法完成，例如，但不限于，从（产品）管直接挤出到膜上，用刮刀在膜上转移和扩散，或用正位移移液器或一次性收集器转移和分配(注意：在给药期间最大限度地减少剪切应力)。应考虑在分配(例如，从产品管)和给药(例如，使用正位移移液器)期间施加在剂型上的剪切应力，并且给药方法应优选以一致的方式，常规最小化控制所有扩散池的剪切应力。同样重要的是，将等量的剂型均匀地施用于膜上，不带气穴，使制剂形成紧凑的圆柱体。产品在膜上的扩散表面积需要保持一致和良好的控制，因为它是计算释放速率的一个因素。应封闭供体隔室，以避免挥发性成分(包括水)从与膜接触的剂型中蒸发，因为蒸发变质可能导致药物组成的变化，并可能改变其线性(稳态)药物释放动力学。

The selection of the receptor solution is guided by the solubility of the drug substance(s) in potential solvents/solvent combinations. Most commonly, combinations of aqueous and alcoholic/organic solvents are used, and the solubility of the drug in the receptor solution should exceed the highest sample concentration in the IVRT study, ideally by an order of magnitude,  but demonstrably sufficient to facilitate a linear (steady state) release rate for the duration of the study (even when evaluating a relatively higher release rate of a formulation that is 150% of the nominal reference strength).

受体溶液的选择取决于原料药在潜在溶剂/溶剂组合中的溶解度。最常见的是，使用水溶剂和酒精/有机溶剂的组合，并且药物在受体溶液中的溶解度应超过IVRT研究中的最高样品浓度，理想情况下要超过一个数量级，但要证明足以促进研究期间的线性(稳态)释放率(即使评估一个相对较高的释放率，即标称参考剂量强度的150%)。

The receptor solution should be adequately mixed, typically by stirring at a constant and well-controlled speed throughout the experiment. The stirring speed or the flow rate should also be part of system qualification and is further described under Equipment.

受体溶液应充分混合，通常在整个实验过程中以恒定和控制良好的速度搅拌。搅拌速度或流量也应是系统鉴定的一部分，并在设备中作进一步说明。

Another factor to consider is the stability of the drug in the receptor solution at the temperature of the test during the IVRT experiment.

另一个需要考虑的因素是在IVRT实验中药物在测试温度下受体溶液中的稳定性。

The system should be appropriately equilibrated under the predefined experimental conditions prior to the beginning of the IVRT run. No air bubbles should be present in the receptor solution (under the membrane) immediately prior to, or during the experiment; if appropriate, the receptor solution can be degassed. The system temperature (including the membrane surface temperature and the circulating water bath temperature, if applicable) should be stable and well controlled. IVRT membranes can be presoaked with receptor solution prior to assembling in the diffusion cell or equilibrated with the receptor solution in situ within the diffusion cell prior to dosing (e.g., for 30 min at a membrane temperature of 32°) depending upon the method.

在IVRT开始运行之前，系统应在预定的实验条件下适当地平衡。在实验前或实验过程中，受体溶液(膜下)中不应出现气泡;如果合适，受体溶液可以脱气。系统温度(包括膜表面温度和循环水浴温度，如适用)应稳定且控制良好。IVRT膜在装配于扩散池之前可以用受体溶液预浸泡，或者在给药之前用扩散池内的受体溶液原位平衡(例如，在32°的膜温度下30分钟)，具体取决于方法。

The test duration should be suitable to characterize the linear (steady state) drug release kinetics of the product formulation. This is typically demonstrated based upon a sustained steady-state release between 4-6 h. The data obtained during the first hour may not represent the steady-state release kinetics, and for many IVRT methods steady-state release kinetics are calculated based upon timepoints from 1 h onward (e.g., at 1, 2, 3, 4, and 5 h, or at 2, 3, 4, 5, and 6 h). At least 5 sampling time points should be planned to obtain a well-characterized release rate. Sampling durations of at least 4 h are suitable to assess steady-state release rates, whereas shortened (e.g., 2 h) sampling durations may not be representative of the steady-state release kinetics. The specific sampling times may be varied depending on the formulation (e.g., every 30 min, or every hour); however, caution should be taken regarding the precise timing of each sample collection to ensure that sample collections happen within the predefined tolerance range. Samples should be withdrawn within a tolerance of ±15 min or ±2% of the nominal time, selecting the tolerance that results in the narrowest time interval.

试验持续时间应适合于表征产品制剂的线性(稳态)药物释放动力学。这通常是基于4-6小时之间的持续稳态释放来证明的。在第一个小时内获得的数据可能不代表稳态释放动力学，并且对于许多IVRT方法，稳态释放动力学是基于从1小时开始的时间点计算的(例如，在1、2、3、4、5小时，或在2、3、4、5和6小时)。应该设计至少5个采样时间点，以获得表征良好的释放速率。至少4小时的采样持续时间适合于评估稳态释放速率，而缩短的采样持续时间(例如2小时)可能不能代表稳态释放动力学。具体采样时间可根据配方而变化(例如，每30分钟或每小时);但是，应注意每次样品采集的精确时间，以确保样品采集在预定义的公差范围内进行。样品应在标称时间的±15分钟或±2%的公差范围内提取，选择产生最小时间间隔的公差。

Sampling is dependent upon the equipment used and should follow instructions provided by the manufacturer, when appropriate. The receptor solution used to replace the volume removed during sampling may be pre-warmed to the temperature of the receptor solution in the receptor compartment, and it is important to ensure that air bubbles are not present beneath the membrane after sampling and refilling the receptor solution at each time point.

抽样取决于所使用的设备，在适当情况下应遵循制造商提供的说明。可以使用经过预热到与反应釜中受体温度一致的受体溶液，用于替代采样过程中去除的样品体积受体溶液，并且重要的是要确保在采样和在每个时间点重新填充受体溶液后膜下不存在气泡。

The test is often conducted with a group of 6 or 12 cells per test run. The results from 6 diffusion cells dosed with a specific product are routinely sufficient to characterize the performance (release rate) of that product using that specific IVRT method. In instances when two products are compared, the results from 6 cells of a test product are often compared with the results from 6 cells of a reference product during the first stage of data analysis. See Data Reporting for more details on the use of additional replicates in instances when a second stage of testing is performed in a comparative IVRT study.

每次测试运行通常使用6或12个单元进行测试。用特定产品给药的6个扩散池的结果通常足以用特定的IVRT方法表征该产品的性能(释放率)。在比较两种产品的情况下，在数据分析的第一阶段，通常将测试产品的6个单元的结果与参考产品的6个单元的结果进行比较。有关在比较IVRT研究中进行第二阶段测试时使用额外重复的更多详细信息，请参见数据报告。

The test is conducted at 32 ± 1° for products applied to the skin (measured at the surface of the membrane, when possible, or inferred based upon the temperature of the receptor solution for immersion cells or VDC Model A). The test is conducted at 37 ± 1° for products intended for internal application (e.g., rectal and vaginal products).

应用于皮肤的产品在32±1°温度下进行测试(如果可能，在膜表面测量，或根据浸没池或VDC模型A的受体溶液的温度推断)。用于内部应用的产品(例如，直肠和阴道产品)在37±1°温度下进行测试。

During the entire test, the nominal system conditions, like the temperature of the receptor solution, should be maintained so that the temperature at the membrane remains within specified parameters (e.g., 32 ± 1°) for the duration of the IVRT. The temperature control qualification is described under Equipment.

在整个测试过程中，应保持标称系统条件，如受体溶液的温度，使膜上的温度在IVRT期间保持在规定的参数范围内(例如，32±1°)。温度控制鉴定在设备一节中描述。

For each cell, the amount of drug released (typically in µg/cm2) at each sampling time (t1, t2, etc.) is determined, and the cumulative amount released is plotted versus √t. The slope of the resulting line is a measure of the rate of drug release.

对于每个池，测定每个采样时间(t1、t2等)的药物释放量(通常以µg/cm2为单位)，并绘制累积释放量与√t的关系。所得直线的斜率是药物释放速率的量度。

For each cell, the individual amount of drug released is plotted versus the square root of time. The slope of the resulting line is the rate of drug release.

对于每个池，单独的药物释放量与时间的平方根成曲线。所得直线的斜率为药物释放速率。

IVRT is a useful tool during semisolid product development to assess whether there may be differences in the arrangement of matter within the semisolid product matrix of compositionally identical (or similar) test and reference products, which may alter their rates of drug release, and that may have the potential to alter product performance in clinical use. When test and reference products exhibit equivalent drug release rates based upon a validated IVRT method, it can mitigate the risk of potential differences in product performance. Therefore, evidence from an IVRT can support a demonstration of bioequivalence, along with other evidence that collectively mitigates the risk of a difference in product performance between a reference product and a prospective generic (test) product.

在半固体产品开发过程中，IVRT是一种有用的工具，用于评估在组成相同(或相似)的测试产品和参考产品的半固体产品基质中物质的排列是否存在差异，这可能会改变它们的药物释放速度，并且可能有可能改变临床使用中的产品性能。当测试品和参比品根据经过验证的IVRT方法显示出相同的药物释放率时，它可以减轻产品性能潜在差异的风险。因此，来自IVRT的证据以及其他证据一起可以支持生物等效性的证明，共同降低了参考产品与预期仿制(试验)产品之间产品性能差异的风险。

IVRT is commonly used to assess the sameness of a drug product after postapproval changes. Because common testing artifacts, such as air bubbles and membrane defects, yield measurements that are not normally distributed, a nonparametric statistical technique is used to evaluate the test results. The Mann-Whitney U test is used to calculate the 90% confidence interval for the ratio of the slopes between the test and the reference batches. This is illustrated by the following example in which the initial drug product batch is referred to as the reference batch (R) and the changed or subsequent batch is referred to as the test batch (T). The individual amounts of drug released from R are plotted versus the square root of time, and the resulting slopes are determined. Those are the reference slopes. The process is repeated for the test batch (T).

IVRT通常用于评估药品批准后变更后的一致性。由于常见的测试工件，如气泡和膜缺陷，产生的测量结果不是正态分布的，因此使用非参数统计技术来评估测试结果。Mann-Whitney U检验用于计算试验批次与参考批次之间斜率之比的90%置信区间。下面的例子说明了这一点，其中初始药品批次被称为参考批次(R)，改变或后续批次被称为测试批次(T)。从R中释放的单个药物量与时间的平方根相对应，并确定了结果斜率。这些是参考斜率。对测试批次(T)重复此过程。

The T/R slope ratios are calculated for each test-to-reference combination of all pairs of T/R slopes. This procedure is facilitated with a table where the values for the slopes for T are listed down the left side of the table and the slopes for R are listed across the top of the table. The T/R slope ratios are then determined. See Table 1.

计算每次试验相对于参考坡度的T/R斜率比。该程序通过一个表格来实现，其中测试批次和参考批次的斜率值分别列在表格的左侧和顶部。然后确定T/R斜率。见表1。

After the T/R ratios have been calculated, they are ordered from the lowest to the highest. The 8th and 29th T/R ratios are identified and converted to percent (multiplied by 100). These values represent the 90% confidence interval for the ratio of test to reference release rates. To pass first stage testing, those ratios must be within the range of 75%–133.33%.

**在计算出T/R比后，它们按从低到高的顺序排列。识别第8和第29个T/R比率并将其转换为百分比（乘以100）。这些值代表试验与参考释放率之比的90%置信区间。要通过第一阶段测试，这些比率必须在75%-133.33%的范围内。**

If the results do not meet this criterion, 4 additional tests (2 reference and 2 test) of 6 cells each should be performed, resulting in 12 additional slope determinations for each product tested. The T/R slope ratios for all 18 slopes for each product tested are determined. All 324 individual T/R slope ratios are ordered from the lowest to the highest. To pass this second stage testing, the 110th and 215th slope ratios, representing the 90% confidence interval, must be within the range of 75%–133.33%.

**如果结果不符合此标准，则应执行4个额外的测试(2个参考和2个测试)，每个测试6个单元，从而为每个测试产品进行12个额外的斜率测定。确认了每个测试样品的所有18个T/R斜率比率。所有324个单独的T/R斜率比从低到高排序。为了通过第二阶段的测试，代表90%置信区间的第110和215斜率比率必须在75%-133.33%的范围内。**

The in vitro permeation test (IVPT) is intended to characterize the rate and extent to which a drug applied on the surface of a biological membrane permeates into and through it, using method parameters aimed to simulate in vivo conditions. IVPT methods can utilize a variety of biological membranes, including excised human skin, which can exhibit natural variations in permeability that are reflective of the variability observed in vivo. This variability can be substantial; it is not uncommon to observe a 10-fold difference in skin permeability for a given compound (in the same formulation) between individuals in the population or between different anatomical regions on the same individual. Experimental variability may also be a result of the physicochemical properties of a molecule. For all products or treatments compared in an experiment, the replicate skin sections used should be sourced from the same donor (or the same set of donors), the same anatomical site (e.g., abdomen, back, etc.), the same source (e.g., elective surgery or cadavers) and manner of preparation (e.g., dermatoming, freezing, etc.) to minimize variability.

体外渗透试验(IVPT)旨在利用旨在模拟体内条件的方法参数，表征应用于生物膜表面的药物渗透到生物膜中的速率和程度。IVPT方法可以利用多种生物膜，包括切除的人体皮肤，其渗透性可以表现出自然变化，这反映了体内观察到的可变性。这种可变性可能是实质性的;在人群中的个体之间或同一个体的不同解剖区域之间，观察到给定化合物(在同一配方中)的皮肤渗透性有10倍的差异并不罕见。实验变异性也可能是分子的物理化学性质的结果。对于实验中比较的所有产品或治疗方法，所使用的重复皮肤切片应来自同一供体(或同一组供体)、相同的解剖部位(如腹部、背部等)、相同的来源(如择期手术或尸体)和制备方式(如剥皮、冷冻等)，以尽量减少可变性。

An IVPT study can be sensitive and discriminating to differences in the rate and extent to which compounds applied on the skin from different formulations become available in and through it. Notably, unlike an IVRT study, differences in permeation that are observed in an IVPT study comparing a test versus reference product, if any, may correlate with and/or be predictive of differences in bioavailability in vivo. The IVPT is routinely carried out to guide semi-solid topical formulation development.

IVPT研究可以对不同配方的涂抹在皮肤上的化合物在皮肤内和通过皮肤获得的速率和程度的差异进行敏感和区分。值得注意的是，与IVRT研究不同的是，在IVPT研究中观察到的比较测试品与参考产品的渗透差异(如果有的话)可能与体内生物利用度差异相关和/或预测了差异。IVPT通常用于指导半固体外用制剂的开发。

IVPT method development should encompass key aspects that influence the IVPT results (some of these aspects are discussed below), including the bioanalytical methodology used to quantify the amount of the drug in the IVPT study samples. The scope of the IVPT method development is dependent upon the purpose of the study. For example, a bioequivalence study is likely to require a larger number of skin donors in order to adequately power a statistical analysis, compared to a study intended to qualitatively evaluate different formulation prototypes. Further, whereas IVPT studies designed to support a demonstration of bioequivalence generally rely upon assessments of the rate and extent to which drugs permeate the skin based upon receptor solution results, the selection of new chemical entities or formulation prototypes may also employ assessments of tissue distributions. A comprehensive discussion on IVPT method validation is outside of the scope of this chapter.

IVPT方法的开发应包括影响IVPT结果的关键方面(其中一些方面将在下文讨论)，包括用于量化IVPT研究样本中药物量的生物分析方法。IVPT方法开发的范围取决于研究的目的。例如，与旨在定性评估不同制剂原型的研究相比，生物等效性研究可能需要更多的皮肤供体，以便充分支持统计分析。此外，虽然IVPT研究旨在支持生物等效性的证明，通常依赖于基于受体溶液结果对药物渗透皮肤的速率和程度的评估，但选择新的化学实体或配方原型也可能采用组织分布的评估。关于IVPT方法验证的全面讨论超出了本章的范围。

Dermatomed human skin (split-thickness, typically around 250–500 µm), sourced from cadavers or elective surgery (typically abdominoplasties or breast reductions), is often the most appropriate membrane of choice due to its intrinsic relevance to a human drug product development, as well its ease of handling during experimental procedures. The thickness of the dermatomed skin should be confirmed prior to assembling the membrane in the diffusion cell, as significant variability in thickness may increase the variability of IVPT results. Epidermal preparations (sheets of epidermis that have been separated from the dermis at the dermal-epidermal junction) require technical experience to process, have less structural integrity compared to dermatomed skin, and may tear or lose barrier integrity more easily. However, epidermal preparations are often more consistent in thickness than dermatomed skin, and the magnitude of permeation for some compounds may be greater through epidermal preparations than through dermatomed skin. Therefore, while dermatomed skin is a good choice to evaluate in most cases, in some situations (e.g., when the drug of interest is not feasible to quantify permeating through dermatomed skin) epidermal preparations may be useful to evaluate during IVPT method development.

离体皮肤（分裂厚度通常在250~500μm左右），其来源通常是尸体或选择性手术(通常是腹部整形或乳房缩小) ，由于其与人类药物产品开发的内在相关性，以及在实验过程中易于处理，是最合适的膜选择。在将膜组装到扩散池中之前，应确认皮肤的厚度，因为厚度的显著变化可能会增加IVPT结果的可变性。表皮制剂(在真皮-表皮交界处从真皮层分离出来的表皮片)需要技术经验来加工，与皮肤相比，其结构完整性较差，并且可能更容易撕裂或失去屏障完整性。然而，表皮制剂在厚度上往往比表皮化的皮肤更一致，并且某些化合物通过表皮化的制剂的渗透幅度可能比通过表皮化的皮肤更大。因此，虽然在大多数情况下，离体皮肤是一个很好的评估选择，但在某些情况下(例如，当感兴趣的药物无法量化通过皮肤的渗透时)，表皮制剂可能有助于在IVPT方法开发过程中进行评估。

Dermatomed porcine skin has a relatively similar morphology to human skin and can be used as a secondary option (as a surrogate for human skin) for research and development studies, unless regulatory guidance recommendations specify otherwise. The use of rodent skin (as a surrogate for human skin) is discouraged due to significant dissimilarity to human skin in terms of morphology and stratum corneum structure and thickness, which can make the results difficult to interpret in terms of their relevance to human skin permeation. The use of cultured skin constructs (reconstructed human epidermis) is not ideal as a surrogate for natural excised human skin because the permeability properties of such tissues is currently not representative of excised human skin. The use of any synthetic membrane (including the types developed to emulate a biological membrane) is not appropriate for an IVPT method; the results of tests with any synthetic membrane may not reflect the rate and extent to which a drug permeates into and through skin and may be misleading.

猪皮具有与人类皮肤相对相似的形态，可作为研究和开发研究的次要选择(作为人类皮肤的替代品)，除非监管指导建议另有规定。不鼓励使用啮齿动物皮肤(作为人类皮肤的替代品)，因为在形态学和角质层结构和厚度方面与人类皮肤有很大的不同，这可能使结果难以解释其与人类皮肤渗透的相关性。使用离体培养的皮肤结构(重建的人表皮)作为天然切除的人皮肤的替代品并不理想，因为这种组织的渗透性目前还不能代表离体人皮肤。使用任何合成膜(包括用于模拟生物膜的类型)都不适合IVPT方法;任何合成膜的测试结果都可能不能反映药物渗透到皮肤的速度和程度，并可能产生误导。

The use of human or porcine full-thickness (non-dermatomed) skin can pose experimental challenges and is generally not recommended. Other membranes such as rectal, vaginal, or corneal epithelial tissue may also be employed, depending on the intended route of administration for the drug product under evaluation. In such circumstances, several parameters of the test method may differ from those used for an IVPT with skin due to specific considerations for modeling the relevant in vivo conditions. For example, the appropriate temperature at which to maintain the membrane may be different.

使用人或猪的全层(非剥皮)皮肤可能会带来实验挑战，通常不建议使用。其他膜，如直肠、阴道或角膜上皮组织也可以使用，这取决于所评估药物的预期给药途径。在这种情况下，由于对相关体内条件建模的具体考虑，测试方法的几个参数可能与用于皮肤IVPT的测试方法不同。例如，维持膜的适当温度可能是不同的。

Two types of diffusion cells are commonly used for IVPT studies: the vertical diffusion cell (VDC) (see Figures 1–5) and the flow-through diffusion cell (FDC) (see Figures 8–10). Equipment features (e.g., bubble-free cells or cells with a vent hole) other than the ones depicted below may be suitable once qualified. VDCs are well characterized and can be utilized for both, IVRT and IVPT studies. FDCs are used exclusively for IVPT studies (not IVRT studies) and have the advantage that the sampling is more easily automated, which can make it easier to acquire samples at times when investigators are typically not in the laboratory (e.g., the middle of the night). VDCs and FDCs can both produce excellent results when the IVPT method is appropriately developed, and each type of cell has its advantages.

**两种类型的扩散池通常用于IVPT研究:垂直扩散池(VDC)(见图1-5)和流通扩散池(FDC)(见图8-10)。除了下面描述的设备特征(例如，无气泡池体或带有排气孔的池体)，一旦合格，可能也适用。VDC具有良好的特征，可用于IVRT和IVPT研究。FDC专门用于IVPT研究(而不是IVRT研究)，其优点是采样更容易自动化，这可以使研究人员通常不在实验室(例如，半夜)时更容易获取样本。当IVPT方法得到适当的发展时，VDC和FDC都可以产生优异的结果，每种类型的池体都有其优点。**

The choice of analytical method should consider the physicochemical properties of the analyte(s) present in the formulation and the actual formulation composition; these factors combined will directly affect the ability of a drug to cross the stratum corneum, therefore impacting drug concentrations in each skin layer and in the receptor solution. Liquid chromatography (LC) coupled with a mass spectrometer (MS) or a tandem mass spectrometer (MS/MS) detector provides excellent sensitivity and selectivity, albeit at the expense of higher complexity in terms of method development/validation, troubleshooting, and higher maintenance costs. LC coupled with an ultraviolet (UV) detector, diode array detector (DAD), or fluorescence detector (FLD) offers lesser technical complexity but is generally less sensitive and can pose selectivity challenges for analytes present in biological samples.

分析方法的选择应考虑制剂中存在的分析物的物理化学性质和实际制剂组成;这些因素结合起来将直接影响药物穿过角质层的能力，从而影响每层皮肤和受体溶液中的药物浓度。尽管在方法开发/验证，故障排除和更高的维护成本方面具有更高的复杂性，液相色谱(LC)与质谱仪(MS)或串联质谱仪(MS/MS)检测器耦合提供了出色的灵敏度和选择性。LC与紫外线(UV)检测器，二极管阵列检测器(DAD)或荧光检测器(FLD)耦合提供较少的技术复杂性，但通常灵敏度不够，并且可能对生物样品中存在的分析物构成选择性挑战。

The use of validated bioanalytical methods with multipoint calibration curves is encouraged. The validation of an analytical method for IVPT sample analysis is done separately from the validation of an IVPT method, each of which follow specific procedures not described in this chapter.

鼓励使用经过验证的具有多点校准曲线的生物分析方法。IVPT样品分析分析方法的验证与IVPT方法的验证是分开进行的，每一个都遵循本章未描述的特定程序。

**试验设计**

Experimental Design

The thermodynamic activity of the drug(s) present in a formulation will affect the rate and extent of skin permeation. It is prudent to understand the drug(s) solubility in the solvents/excipients of interest, as well as in the formulation prototypes under evaluation.

制剂中存在的药物的热力学活性将影响皮肤渗透的速率和程度。谨慎的做法是了解药物在所用的溶剂/赋形剂中的溶解度，以及在评估中的原型制剂中的溶解度。

The finite dose typically ranges from 2–15 mg of formulation per square centimeter of dosing area, with a dose of 5–10 mg/cm2 often used as a starting dose for method development. Ensuring consistency in the dispensing of the formulation (e.g., from the product tube) and uniform dose administration (spreading/coverage) on the skin section placed in the diffusion cell can help minimize experimental variability. The use of positive-displacement pipettes is recommended to ensure dosing precision. For semisolid dosage forms such as ointments, creams, and certain gels that do not flow like a solution, a glass rod or the bottom of a glass vial can be used to evenly spread the formulation within the dosing area.

有限剂量通常为每平方厘米给药面积含2-15mg制剂，剂量为5-10mg /cm2常作为方法开发的起始剂量。确保配方分配的一致性(例如，从产品管中)和在放置在扩散池中的皮肤部分上的均匀剂量给药(扩散/覆盖)可以帮助最小化实验变异性。建议使用正位移移液器，以确保加药精度。对于半固体剂型，如软膏、面霜和某些不像溶液那样流动的凝胶，可使用玻璃棒或玻璃小瓶底部将制剂均匀地散布在给药区域内。

The receptor solution should ensure sufficient solubility of the drug(s) of interest throughout the length of the study, thus not limiting the rate of diffusion/partitioning of the drug(s) from the skin to the receptor solution. The solubility of the drug in the receptor solution should exceed the highest sample concentration in the IVPT study, ideally by an order of magnitude, if possible. The inclusion of 0.1% (w/v) polyoxyethylene (20) oleyl ether is ideal to enhance the solubility of physiological buffer based (aqueous) receptor solutions for hydrophobic drugs. If additional solubility is needed, small increases in the concentration of polyoxyethylene (20) oleyl ether [e.g., from 0.1% (w/v) to 0.2% (w/v)] is typically adequate for most hydrophobic drugs. Higher concentrations of polyoxyethylene (20) oleyl ether may be evaluated, as needed, but should not exceed 6% because higher concentrations may alter the skin barrier. Other solubility modifiers may also be effective but may not be suitable for studies assessed by a regulatory agency unless the impact of that solubility modifier on the permeability of the skin barrier has been adequately characterized. Other strategies to improve the solubility of the drug in the receptor solution that may have the potential to alter the permeability of the skin (e.g., inclusion of organic solvents and alcohols in the receptor solution) are not prudent and may invalidate the IVPT method. Additionally, labile compounds may require modifications in the receptor solution, including the addition of antioxidants and/or chelating agents (e.g., ethylene diamine tetra acetic acid; EDTA) or the use of acidified water (e.g., pH 4.0) instead of phosphate-buffered saline (PBS). The addition of antibacterial/antimycotic agents [e.g., 0.1% (w/v) sodium azide; 0.01% (w/v) gentamicin sulfate] in the receptor solution is also important to prevent microorganism growth and membrane tissue degradation.

受体溶液应确保目标药物在整个研究过程中具有足够的溶解度，从而不限制药物从皮肤到受体溶液的扩散/分配速率。药物在受体溶液中的溶解度应超过IVPT研究中最高的样品浓度，如果可能的话，最好超过一个数量级。0.1% (w/v)聚氧乙烯(20)油基醚的包合是提高生理缓冲液(水)受体溶液对疏水药物的溶解度的理想选择。如果需要额外的溶解度，对于大多数疏水药物来说，聚氧乙烯(20)油基醚浓度的小幅增加[例如，从0.1% (w/v)增加到0.2% (w/v)]通常就足够了。根据需要，可以评估较高浓度的聚氧乙烯(20)油基醚，但不应超过6%，因为较高的浓度可能会改变皮肤屏障。其他溶解度调节剂也可能有效，但可能不适合由监管机构评估的研究，除非该溶解度调节剂对皮肤屏障渗透性的影响已得到充分表征。其他提高药物在受体溶液中的溶解度的策略可能会改变皮肤的渗透性(例如，在受体溶液中包含有机溶剂和醇)，这些策略是不谨慎的，并且可能使IVPT方法无效。此外，不稳定的化合物可能需要在受体溶液中进行修饰，包括添加抗氧化剂和/或螯合剂(例如，乙二胺四乙酸;EDTA)或使用酸化水(例如pH 4.0)代替磷酸盐缓冲盐水(PBS)。添加抗菌/抗真菌剂[例如，0.1% (w/v)叠氮化钠;0.01% (w/v)硫酸庆大霉素]受体溶液对防止微生物生长和膜组织降解也很重要。

The system should be appropriately equilibrated under the predefined experimental conditions prior to the beginning of the IVPT run. No air bubbles should be present in the receptor solution (under the membrane) immediately prior and during the experiment; if appropriate, the receptor solution can be degassed. The system temperature (including the membrane surface temperature and the circulating water bath temperature, if applicable) should be stable and well controlled. Frozen biological membranes should be thawed at ambient temperature prior to assembling on the diffusion cells. Once mounted, the skin sections should be allowed to equilibrate to a physiologically relevant state of hydration and temperature (e.g., for 30 min at a membrane surface temperature of 32°).

在IVPT开始运行之前，系统应在预先确定的实验条件下进行适当的平衡。在实验之前和实验过程中，受体溶液(膜下)中不应出现气泡;如果合适，受体溶液可以脱气。系统温度(包括膜表面温度和循环水浴温度，如适用)应稳定且控制良好。冷冻的生物膜应在室温下解冻，然后组装在扩散池上。一旦安装，皮肤切片应该被允许平衡到生理上相关的水合作用和温度状态(例如，在32°的膜表面温度下30分钟)。

The test duration should be sufficient to characterize a suitable permeation profile. For IVPT studies that are intended to support a demonstration of bioequivalence, the selected sampling schedule and study duration should be sufficient to characterize the cutaneous pharmacokinetics of the drug, which ideally includes a sufficiently complete flux profile to identify the maximum (peak) flux and a decline in the flux thereafter across multiple subsequent time points. IVPT studies typically range from 12–72 h in length; IVPT bioequivalence studies may require longer periods of time to observe a sufficient decline in the skin flux to adequately characterize the cutaneous pharmacokinetics.

测试持续时间应足以表征合适的渗透曲线。对于旨在支持生物等效性证明的IVPT研究，所选择的采样计划和研究持续时间应足以表征药物的皮肤药代动力学，理想情况下包括足够完整的通量概况，以确定此后多个后续时间点的最大(峰值)通量和通量下降。IVPT研究的长度通常为12-72小时;IVPT生物等效性研究可能需要更长的时间来观察皮肤通量的充分下降，以充分表征皮肤药代动力学。

The IVPT method development should support the selection of an appropriate sampling schedule, intended to provide suitable resolution for the flux profile. A study with fewer than 8 nonzero sampling time points may not provide adequate characterization of the flux profile.

IVPT方法的开发应支持选择适当的采样计划，旨在为通量曲线提供适当的分辨率。少于8个非零采样时间点的研究可能无法提供通量分布的充分表征。

Depending on the stage of method development, the number of donors may vary. A study with fewer than 4 donors and 4 replicates per donor per treatment may be difficult to interpret. IVPT bioequivalence studies may require a larger number of donors and replicates to adequately power a statistical analysis. The inclusion of a nondosed control (no formulation) is recommended and may help ensure the skin source(s) and receptor solution are absent of contaminants that may influence the results.

根据方法发展的阶段，皮肤供体的数量可能有所不同。一个研究如果少于4个供体且每次治疗中每个供池有4个单个供体重复可能难以解释实验数据。IVPT生物等效性研究可能需要大量的皮肤供体和单个供体重复，以充分支持统计分析。建议加入非剂量对照(无制剂)，这可能有助于确保皮肤源和受体溶液不含可能影响结果的污染物。

The surface of each skin section should be kept constant at 32 ± 1° throughout the length of the study. Temperature fluctuations of the skin surface will affect drug diffusion and may increase experimental variability. The use of a thermoregulated diffusion cell is encouraged to control the temperature of the membrane surface.

在整个研究过程中，每个皮肤切片的表面应保持在32±1°恒定。皮肤表面的温度波动会影响药物的扩散，并可能增加实验的可变性。鼓励使用具有温控的扩散池来控制膜表面的温度。

The skin barrier integrity in each diffusion cell should be confirmed prior to dosing by using techniques such as transepidermal water loss (TEWL), electrical impedance/conductance or tritiated water permeation; only skin sections with acceptable barrier integrity results should be dosed. TEWL is often a preferred method because, unlike the other methods, it measures the flux of water through the skin barrier while it is dry and in contact with the air, as it is in the normal in vivo state, and TEWL is relatively rapid and convenient.

在给药前，应使用经皮失水(TEWL)、皮肤电阻抗/电导仪或氚化水渗透等技术确认每个扩散池的皮肤屏障完整性;只有具有可接受屏障完整性结果的皮肤切片才能给药。TEWL通常是一种首选的方法，因为与其他方法不同，它测量的是在皮肤干燥并与空气接触时通过皮肤屏障的水通量，因为它是在正常的体内状态，TEWL相对快速和方便。

Most IVPT experiments report skin flux and the total cumulative amount of drug that has permeated into the receptor solution (or as a percentage of drug from the total applied dose). Depending on the purpose of the study, an evaluation of drug tissue distribution (amounts in the stratum corneum, viable epidermis, and dermis) and total mass balance may provide additional insights.

大多数IVPT实验报告皮肤通量和渗透到受体溶液中的药物总累积量(或药物占总应用剂量的百分比)。根据研究的目的，对药物组织分布(角质层、活表皮和真皮层中的药物量)和总质量平衡的评估可能会提供额外的见解。

Full mass balance requires more intensive bioanalytical method development to ensure that the drug(s) of interest are efficiently extracted from each sample matrix type, such as cotton swabs used to remove the excess of formulation present on the skin surface at the end of the experiment, tape strips used to remove stratum corneum, and homogenized viable epidermis and dermis.

完全的质量守衡需要更深入的生物分析方法开发，以确保从每种样品基质类型中有效地提取感兴趣的药物，例如在实验结束时用于去除皮肤表面过量配方的棉签，用于去除角质层的胶带，以及均质活表皮和真皮层。

Epidermis and dermis heat splitting can be accomplished by placing the skin sections (harvested at the end of the IVPT study) on a sheet of aluminum foil and incubating it (dry heat) at 60° for 2–3 min. After this step, the epidermis can be separated (by scraping) from the dermis by using forceps. Because the drug levels in the epidermis are generally higher than the dermis, the splitting should be done carefully to avoid cross contamination, and clean forceps should be used in between samples.

可以通过将皮肤切片(在IVPT研究结束时收获)放在铝箔上并在60°下孵育(干热)2-3分钟来热分裂表皮和真皮层。在这一步之后，可以使用镊子将表皮(通过刮)从真皮层中分离出来。由于表皮中的药物含量通常高于真皮层，因此分离应小心进行，以避免交叉污染，样品之间应使用干净的镊子。

Depending on the purpose of the study (bioequivalence, formulation development, prototype screening, etc.), data may be reported and assessed using different parameters (endpoints). For example: a bioequivalence study will focus on the cutaneous pharmacokinetic endpoints of maximum flux (Jmax), and total cumulative amount (AMT) of drug permeated. Studies conducted in early stages of drug development, such as those intended to select a new chemical entity (NCE), or to rank different formulation prototypes, may report tissue (epidermis and dermis) concentrations in addition to the parameters (endpoints) above, and may include full mass balance data.

根据研究目的(生物等效性、制剂开发、原型筛选等)，可以使用不同的参数(终点)报告和评估数据。例如:生物等效性研究将关注皮肤药代动力学的最大通量终点(Jmax)和药物渗透的总累积量(AMT)。在药物开发的早期阶段进行的研究，例如那些旨在选择新化学实体(NCE)或对不同配方原型进行排序的研究，除了上述参数(终点)外，还可能报告组织(表皮和真皮)浓度，并可能包括完整的质量平衡数据。

The flux (rate of drug permeation) should be calculated for each time point in units of mass/area/time (e.g., ng/cm2/h) on the y-axis versus time in the x-axis. The extent of drug permeation should also be reported in units of mass/area (e.g., ng/cm2) in the y-axis versus time in the x-axis—the slope of this curve can help determine the overall drug flux through the skin at different points in time. Drug levels in the viable epidermis and dermis can be reported as absolute mass amount (e.g., nanograms or micrograms) or concentration (e.g., nanograms or micrograms of drug per milligram of tissue [ng/mg or µg/ mg]).

每个时间点的通量(药物渗透率)应以质量/面积/时间(例如，ng/cm2/h)为单位在y轴上与时间在x轴上进行计算。药物的渗透程度也应在y轴上以质量/面积(例如，ng/cm2)为单位报告，在x轴上以时间为单位报告——该曲线的斜率可以帮助确定在不同时间点通过皮肤的总体药物通量。活的表皮和真皮层中的药物水平可以用绝对质量(例如，纳克或微克)或浓度(例如，每毫克组织中药物的纳克或微克[ng/mg或µg/ mg])来报告。

Full mass balance results are generally reported as percentage of drug(s) in each compartment (e.g., stratum corneum, viable epidermis, dermis and receptor solution) relative to the total amount applied at the beginning of the experiment.

全质量守衡结果通常报告为每个部分(例如角质层、活表皮、真皮层和受体溶液)中药物相对于实验开始时施用的总量的百分比。

The selection between IVRT or IVPT should be based on the intended objective(s) of the formulation assessment, as described in Table 2. Intrinsic experimental differences between the two methodologies are further described in Table 3.

**IVRT或IVPT之间的选择应基于制剂评估的预期目标，如表2所示。表3进一步描述了两种方法内在的实验差异。**

表2.根据目标选择合适的检测方法(IVRT或IVPT)指南

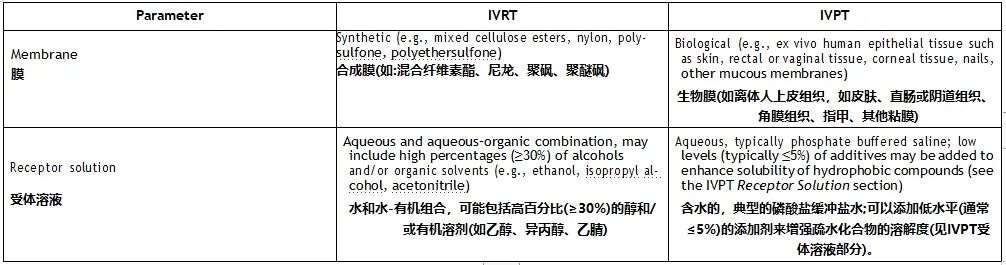


表3.IVRT和IVPT方法的关键区别

表3.IVRT和IVPT方法的关键区别（续表）

**设备**

EQUIPMENT

The VDC, immersion cells, and FDC should match the general descriptions provided below and may have design variations of the types shown among specific examples illustrated in Figures 1–5 for VDCs, Figures 6 and 7 for immersion cells, or Figures 8–10 for FDCs. The VDC, immersion cell, and FDC components should be manufactured with inert materials that do not adsorb, absorb, bind, or react with the analyte. The diffusion cell and its components should not alter the amount of diffusing drug that is measured, either by adsorbing, absorbing, binding, or reacting with the drug, or by releasing drug that was adsorbed, absorbed, bound, or reacted with in a previous experiment.

VDC、浸没池和FDC应符合下面提供的一般描述，并且可以在图1-5所示的VDC、图6和图7所示的浸没池或图8-10所示的FDC的具体示例中具有不同的设计类型。VDC、浸没池和FDC组件应使用惰性材料制造，这些材料不会吸附、吸收、结合或与分析物发生反应。扩散池及其组件不应通过吸附、吸收、结合或与药物反应，或通过释放先前实验中吸附、吸收、结合或与之反应的药物来改变所测量的扩散药物的量。

The operating principles and specific test procedures differ among the various equipment; relevant procedures from the manufacturer may be used for installation, operational, and performance qualifications, if available.

各种设备的工作原理和具体测试程序不同;如果有的话，可以使用制造商的相关程序进行安装、操作和性能确认。

However, regardless of what qualification information is provided by a diffusion cell manufacturer, the laboratory performing the test should perform an initial qualification of each diffusion cell. Qualified diffusion cells can be used in numerous experiments, and do not need to be qualified again (i.e., requalified) each time. The condition of the orifices and diffusion cells should be ascertained prior to each test. Certain diffusion cell components such as O-rings or tubing may require re-evaluation and occasional replacement. Automated systems are too varied to be covered in any detail within this chapter; however, they should be requalified routinely (e.g., every 6-12 months) based on the manufacturers’ recommendations.

然而，无论扩散池制造商提供什么样的确认信息，进行测试的实验室都应该对每个扩散池进行初步确认。合格的扩散池可用于多次实验，不需要每次都再次确认(即重新确认)。每次试验前应确定孔和扩散池的状况。扩散池的某些部件，如o形环或管道，可能需要重新评估和偶尔更换。自动化系统变化太大，本章无法详细介绍;但是，应根据制造商的建议定期(例如每6-12个月)重新确认。

The initial qualification of each diffusion cell should, at minimum, include:

每个扩散池的初始确认至少应包括:

1. Measurements of the diffusional area of the orifices of the donor and receptor compartments between which the membrane is mounted

对放置膜的供体和受体腔室孔的扩散面积的测量

2. Empirically measured volume of the receptor solution compartment/vessel for each VDC or immersion cell, or the empirically measured outflow tube length for each FDC

经验性测量每个VDC或浸没池的受体溶液室/容器的体积，或经验性测量每个FDC的流出管长度

3. Stability of the temperature measured at the membrane surface (e.g., 32 ± 1°) across a relevant duration (e.g., 6 h for IVRT or 48 h for IVPT)

在相关持续时间内(例如，IVRT为6小时或IVPT为48小时)膜表面测量温度的稳定性(例如，32±1°)

4. Rate of stirring or agitation for VDCs or immersion cells, or the flow rate for FDCs, as applicable

VDCs或浸没池的搅拌或搅拌速率，或FDCs的流量，视情况而定

In addition to the quantitative assessments described above, qualitative assessments should verify that diffusion cells do not leak, and that the membrane can be mounted securely in the diffusion cell so that there is no bulk flow of a dosage form from the donor compartment to the receptor compartment that circumvents the membrane. Several other considerations relevant to a well-controlled test may be included in the qualification.

除了上述的定量评估外，定性评估还应验证扩散池不会泄漏，并且膜可以安全地安装在扩散池中，这样就不会有从供体隔室到受体隔室的大量药物绕过膜进入受体隔室。与控制良好的试验有关的其他几个考虑因素也可能包括在确认中。

1. Qualification of Orifice Diameter: The orifice diameter for the donor and receptor compartments can be determined using vernier calipers. The orifice should be inspected for any chips or other damage which may alter the surface area.

孔直径的确认:供体和受体室的孔直径可以用游标卡尺确定。应检查孔口是否有任何可能改变表面面积的碎片或其他损坏。

For immersion cells, the volume of receptor solution to be filled in the dissolution vessel should be accurately measured with the appropriate volumetric glassware and transferred to the dissolution vessel.

对于浸没池，应使用适当体积的玻璃器皿准确测量所用的受体溶液体积，并将其转移到溶出杯中。

3. Qualification of Temperature Control: The temperature of each cell should be equilibrated to provide the target temperature at the membrane, and the initial qualification of the equipment should verify that the temperature can be maintained for the duration of the test when using the relevant equipment and method parameters. Depending on the VDC or FDC equipment design, a measurement of the membrane temperature can often be made conveniently using an infrared thermometer, or using a thermocouple mounted with the membrane; for immersion cells, the temperature at the membrane may be assumed to be the same as the bulk volume of the receptor solution in the dissolution vessel, once equilibrated and stabilized. The temperature of each cell should typically remain within ±1° of the target temperature (typically 32° or 37°) during the test.

温度控制的确认:应平衡每个池体的温度使膜达到目标温度，并且设备的初始确认应验证在使用相关设备和方法参数时，该温度可在测试期间保持。根据VDC或FDC设备的设计，膜温度的测量通常可以方便地使用红外温度计，或使用安装在膜上的热电偶;对于浸没池，可以假设膜上的温度与溶解容器中受体溶液的体积相同，一旦达到平衡和稳定。在测试过程中，每个池体的温度通常应保持在目标温度(通常为32°或37°)的±1°内。

4. Qualification of Stirring/Agitation/Flow Rate: The stirring rate should be verified with a suitable device, such as a photo tachometer. For VDC, stirring rates in the range of 400–600 rpm are common. The stirring rate measured is typically applicable to the specific location where the stirring impeller is (e.g., a specific position in a rack that holds multiple VDC, or a specific stir plate). Stirring rate can be measured using a surrogate stir bar if the stir bar used in the diffusion cell is too small to obtain an accurate measurement. The paddle stirring rate for immersion cells of 50 or 100 rpm is common and should be verified and maintained during the test.

4.（桨法）搅拌/（搅拌子）搅拌/流速的确认:搅拌速率应使用合适的设备进行验证，例如光转速计。对于VDC，搅拌速率范围在400-600 rpm是常见的。测量的搅拌速率通常适用于搅拌叶轮所在的特定位置(例如，在容纳多个VDC的机架中的特定位置，或特定的搅拌板)。如果扩散池中使用的搅拌子太小而无法获得准确的测量，则可以使用替代搅拌子来测量搅拌速率。浸没池的桨叶搅拌速率通常为50或100转/分，在试验期间应加以验证和保持。

Stirring rates are relevant for VDC, but not necessarily for FDC or immersion cells. In case of FDC, the flow rate of the receptor solution should be set at a specific value and maintained throughout the test. The flow rate (typically expressed in units of milliliters per minute) can be determined by setting the desired flow rate and collecting a sample into a tared vial for a specific duration. A suitable flow rate allows for a sample of sufficient size to ensure an accurate weighing and should not be substantially impacted by normal variability that may arise due to a drop that fails to fall from the tip of the dispensing tube. It is essential that the lengths of all the dispensing tubes are exactly the same, because differences in dispensing tube lengths can alter the void volume and lag time for samples to be dispensed into collection tubes.

搅拌速率与VDC有关，但不一定与FDC或浸没池有关。在FDC的情况下，受体溶液的流速应设定在一个特定的值，并在整个测试过程中保持。流速(通常以毫升/分钟为单位表示)可以通过设置所需的流速并在特定时间内将样品收集到带刻度的小瓶中来确定。合适的流量允许足够大小的样品以确保准确称重，并且不应受到由于未能从分配管尖端落下的液滴可能产生的正常变异性的实质性影响。所有分配管的长度必须完全相同，因为管长度的差异会改变样品被分配到收集管中的空隙体积和滞后时间。

A VDC consists of two compartments (a donor compartment and a receptor compartment with a sampling arm) separated by a membrane and held together by a clamp, screw top, or other means (see Figures 1–5). The VDC body (i.e., donor and receptor compartment with associated cell structures like the sampling arm and water jacket, if present) is usually made from borosilicate glass, although different materials may be used to manufacture the body and other parts of the VDC assembly. Other diffusion cells that are similar in design principles and features to those depicted in Figures 1–3 can generally be used.

VDC由两个隔室(供体隔室和带采样臂的受体隔室)组成，隔室由膜隔开，并通过夹钳、螺旋顶或其他方式连接在一起(见图1-5)。VDC主体(即，供体和受体隔室与相关的池体结构，如采样臂和水套，如果存在)通常由硼硅酸盐玻璃制成，尽管可以使用不同的材料来制造主体和VDC组件的其他部分。通常可以使用与图1-3所示扩散池在设计原理和特征上相似的其他扩散池。

The diameters of the orifices of the donor compartment and receptor compartment, which influence the diffusional area for the test, should be sized within ±5% of the specified diameter. The diameter of the donor and receptor compartment orifices may vary for different diffusion cell models. The receptor compartment orifice should be the same size as the donor compartment orifice. The design of the VDC should facilitate proper alignment of the orifices in the donor and receptor compartments. The membrane should be held in a horizontal plane between the donor and receptor compartments. Also, the membrane should be mounted so that it is flat, with no folds or wrinkles. The receptor compartment in each unit of a given model of VDC should be manufactured consistently, with a uniform height and geometry. All the cells (units) of the same VDC model should have the same nominal volume, and the actual volume should be measured and recorded for each individual cell. Care should be taken to minimize the intercell volume variability (e.g., not more than ±5%).

供体腔室和受体腔室的孔直径影响试验的扩散面积，其尺寸应在规定直径的±5%范围内。对于不同的扩散池模型，供体和受体腔室孔的直径可能不同。受体腔室孔应与供体腔室孔大小相同。VDC的设计应有利于供体和受体腔室孔的适当对齐。膜应保持在供体和受体间室之间的水平面上。此外，膜应该安装，使其平整，没有褶皱或皱纹。给定VDC模型的每个单元中的受体隔室应一致制造，具有统一的高度和几何形状。同一VDC型号的所有池(单元)应具有相同的标称体积，并应测量和记录每个单独池体的实际体积。应注意尽量减少池体间体积变化(例如，不超过±5%)。

When conducting IVRT or IVPT studies, the VDC units are typically positioned in a stirrer rack (not depicted) that holds multiple VDC units (e.g., in sets of 6 or 7) in the correct orientation, providing magnetic stirring at a calibrated rate.

在进行IVRT或IVPT研究时，VDC单元通常位于搅拌器机架(未描述)中，该搅拌器机架以正确的方向容纳多个VDC单元(例如，一组6个或7个)，以校准的速率提供磁搅拌。

A magnetic nonstick (e.g., Teflon-coated), inert stir bar or similar stirring/agitation device in the receptor compartment is used as the internal stirring mechanism. The stirring bar or device should provide enough circulation to ensure contents of the receptor compartment are uniform. Samples of the receptor solution are removed at intervals throughout the test, and regardless of whether the entire receptor compartment volume or only an aliquot is sampled, an equivalent volume of stock receptor solution is replaced at each sampling event. The aliquots should be removed from the well-mixed center of the receptor compartment, unless sufficient proof exists that the entire receptor solution volume, including the portion in the sampling arm, are homogeneous and at the same concentration. For most VDC models, it is ideal for the volume of receptor solution in the sampling arm to be sampled and dispensed (repeatedly, a few times) into the well-mixed center of the receptor compartment, to ensure that the entire volume of the receptor compartment is homogeneous.

磁性不粘(例如，特氟龙涂层)的惰性搅拌子或类似的搅拌装置在受体室被用作内部搅拌机构。搅拌子或装置应提供足够的水循环，以确保受体室的内容物均匀。在整个测试过程中，每隔一段时间取出受体溶液的样品，无论取样的是整个受体隔室的体积还是只取样一部分，每次取样时都要更换等量的受体溶液。除非有充分证据证明整个受体溶液体积(包括取样臂中的部分)均质且浓度相同，否则应将样品从混合良好的受体室中心取出。对于大多数VDC模型，理想的情况是采样臂中的受体溶液体积被采样并分配(重复，几次)到混合良好的受体室中心，以确保受体室的整个池体中的样品是均匀的。

Observational checks should be performed prior to testing. The donor and receptor compartment orifices should be evaluated for any chips or other damage which may affect the orifice area. Chipped or damaged cells should not be used.

在测试之前应该进行观察性检查。应评估供体和受体腔室孔口是否有任何碎片或其他可能影响孔口区域的损伤。切屑或损坏的池体不应使用。

It is conventional to install the membrane and then fill the receptor compartment with receptor solution. Any bubbles present underneath the membrane should be removed by tipping the cell and allowing the bubble to rise through the arm.

传统的做法是先安装膜，然后用受体溶液填充受体腔室。任何存在于膜下的气泡都应该通过翻转池体，让气泡从斜臂上升来去除。

The system should be equilibrated, and the temperature should be measured at the membrane. The membrane should be within ±1° of the target temperature (typically 32° or 37°) prior to applying the dosage form. The stirrers should be turned on during the equilibration period.

系统应平衡，并在膜处测量温度。在上样之前，膜应在目标温度(通常为32°或37°)的±1°范围内。在平衡期间应打开搅拌子搅拌。

For specific dosing techniques to apply the product to the membrane, refer to In Vitro Release Test (IVRT), Experimental Design, Dose.

有关将产品应用于膜上的具体给药技术，请参阅体外释放试验(IVRT)，实验设计，剂量

Model A VDC are intended to have the membrane prepared and the dosing performed as part of the assembly of the cell top, which is separate from the cell bottom of the Model A VDC. In this model, the unique design and operation of the Model A VDC, as defined by the manufacturer, should be taken into consideration along with requirements of the test method. This method should not be used with conventional VDC designs like VDC models B and C.

A型VDC的目的是将膜的制备和给药作为池体顶部组装的一部分进行，池体顶部与A型VDC的池体底部分开。在本模型中，应考虑制造商定义的A型VDC的独特设计和操作，以及测试方法的要求。这种方法不应用于传统的VDC设计，如VDC模型B和C。

During the preparation and dosing of the membrane in the Model A VDC cell top assembly, the membrane should be placed below the Model A VDC donor compartment’s dosage wafer on a flat and firm surface. The dosage form is then applied to the membrane within the dosage wafer. The Model A VDC donor compartment (dosage wafer) is filled to capacity; a small spatula can be used to dispense and spread the dosage form evenly within the dosage wafer and to remove any excess formulation.

在A型VDC池顶部组件中膜的制备和给药过程中，膜应放置在A型VDC供体室的定量环下方的平坦坚固的表面上。然后将所述药物施用于所述定量环内的膜上。A型VDC供体室(定量环)被填满;可使用小抹刀在定量环内均匀地分配和涂抹药物，并去除任何多余的制剂。

The receptor compartment of the Model A VDC should be filled with receptor solution that is equilibrated to the target temperature (typically 32° or 37°) during the preparation and dosing of the membrane in the cell top assembly. The stirrers can be run during this period to speed up temperature stabilization. The receptor solution temperature should be measured and ensured to be within ±1° of the target temperature prior to mounting the cell top assembly. The stirrers can be run to help speed up temperature stabilization.

A型VDC的受体室应充满受体溶液，在池体顶部组装膜的制备和给药过程中，受体溶液应平衡到目标温度(通常为32°或37°)。在此期间可以运行搅拌子以加速温度稳定。在安装池体顶部组件之前，应测量并确保受体溶液温度在目标温度的±1°范围内。搅拌子可以运行，以帮助加快温度稳定。

To start the test, the donor compartment cell top assembly is mounted on the cell bottom assembly of the Model A VDC so that the membrane is facing the receptor compartment, and the membrane separates the dosage form from the receptor solution. After assembly of the Model A cell top and bottom, the fully assembled cell should be checked to ensure that no bubbles are present underneath the membrane, and that the membrane has not slipped out of position whereby the dosage form might flow directly into the receptor compartment, circumventing the membrane.

为了开始测试，将供体隔室池体顶部组件安装在A型VDC的池底部组件上，使膜面向受体隔室，膜将药物与受体溶液分离。在A型池体的顶部和底部组装完成后，应检查完全组装的池体，以确保膜下没有气泡存在，并且膜没有滑出位置，否则药物可能会绕过膜直接流入受体室。

VDC are typically sampled one of two ways for IVRT, either withdrawal and replacement, or displacement. Cells which use withdrawal and replacement will typically only have one arm leading to the receptor compartment. Cells which are sampled by displacement will have two arms leading to the receptor compartment. For cells sampled by different methods it is recommended to refer to the manufacturer’s documentation.

对于IVRT, VDC通常有两种采样方式，要么提取和替换，要么替代。使用提取和替换的池通常只有一条通向受体室的臂。通过替代取样的池体将有两条臂通向受体室。对于用不同方法取样的池体，建议参考制造商的文档。

The receptor solution volume in the arm of many VDC may not mix adequately with the volume of receptor solution in the stirred receptor compartment. To ensure that the entire volume of the receptor compartment is homogeneous, it is ideal for the volume of receptor solution in the sampling arm to be sampled (drawn out) from the arm and re-dispensed into the well-mixed center of the receptor compartment multiple times prior to collecting a sample of the receptor solution for analysis. A precise volume of the sample should be withdrawn from the well-mixed center of the receptor compartment, typically using a precise syringe or pipette. Typical sample amounts are 200 to 500 µL. The same amount of receptor solution is then replaced through the same arm. Care should be taken to ensure that a bubble is not introduced during the sampling withdrawal and replacement process. If a bubble is present, it should be removed by tipping the cell and guiding the bubble up the arm. Depending upon the test method, the stirring may continue throughout the sampling procedure, or prior to the sample time point, the stirring may be stopped and then resumed shortly after the volume of receptor solution is replaced.

许多VDC臂中的受体溶液体积可能无法与搅拌后的受体室中的受体溶液体积充分混合。为了确保受体腔室的整个体积是均匀的，在收集受体溶液样品进行分析之前，理想的做法是将取样臂中的受体溶液体积从取样臂中取样(抽出)并多次重新分配到混合良好的受体腔室中心。通常使用精确的注射器或移液器，从混合良好的受体隔室中心抽取精确体积的样品。典型的样品量为200至500µL。同样数量的受体溶液通过同样的斜臂被替换。在取样提取和更换过程中应注意确保不产生气泡。如果出现气泡，应该通过倾斜池体并引导气泡向上移动到斜臂来去除气泡。根据测试方法的不同，搅拌可以在整个取样过程中继续进行，或者在取样时间点之前，搅拌可以停止，然后在替换受体溶液体积后不久重新开始。

Cells with two sampling arms are often sampled by displacement. Prior to the sample time point, all stirring is stopped. The replacement receptor solution is slowly added to the receptor compartment to prevent mixing. The receptor solution displaces the sample out the other sampling arm for collection. Once the sample is collected the stirring is resumed. Typically, a rinse volume is required in the process for displacement sampling to ensure that the current sample does not contain remnants of a previous sample. This is especially important for automated systems.

具有两个采样臂的池体通常通过替代进行采样。在样品时间点之前，停止所有搅拌。将替代受体溶液缓慢加入受体室以防止混合。受体溶液将样品从另一个采样臂中置换出来进行收集。样品收集好后，继续搅拌。通常，替代取样过程中需要一定的漂洗量，以确保当前样品不含有先前样品的残留物。这对自动化系统尤其重要

Observational checks should be performed prior to testing. The donor and receptor compartment orifices should be evaluated for any chips or other damage which may affect the orifice area. Chipped or damaged cells should not be used.

在测试之前应该进行观察性检查。应评估供体和受体腔室孔口是否有任何碎片或其他可能影响孔口区域的损伤。有缺口或损坏的池体不应使用。

Receptor solution can either be preheated or allowed to equilibrate to temperature in the receptor compartments of the diffusion cells.

受体溶液既可以预热，也可以在扩散池体的受体室中平衡温度

Skin should be cut to the appropriate size for the diffusion cell (larger than the diffusional area of the orifice) to ensure that the orifice is completely covered.

皮肤应切割成适合扩散池的尺寸(大于孔的扩散面积)，以确保孔被完全覆盖。

Ideally, the skin should be gently stretched to ensure that it is flat (with no folds or wrinkles) when mounted upon the diffusion cell with the stratum corneum of the skin facing toward the air. An inert support membrane (i.e., a synthetic membrane validated for use with an IVRT method for the same drug product) may be used beneath the skin, as appropriate, as long as it does not impede the diffusion of the drug from the skin to the receptor solution. The donor compartment should then be installed on top of the skin ensuring that the skin is mounted securely in the diffusion cell. The receptor compartment may be filled with receptor solution either before or after mounting of the skin. Any bubbles underneath the skin should be removed by tipping the cell and guiding the bubble up the sampling arm. The thermoregulatory mechanism of the VDC system should then be utilized to equilibrate the skin to the target temperature.

理想情况下，皮肤应该被轻轻拉伸，以确保它是平坦的(没有褶皱或皱纹)，当安装在扩散池上时，皮肤的角质层面向空气。只要不妨碍药物从皮肤向受体溶液的扩散，可酌情在皮肤下使用惰性支撑膜(即，经IVRT方法验证可用于同一药物制品的合成膜)。然后应将供体隔室安装在皮肤的顶部，确保皮肤安全地安装在扩散池中。受体隔室可以在皮肤安装之前或之后充满受体溶液。皮肤下的任何气泡都应该通过倾斜池体并引导气泡向上取样臂来去除。然后利用VDC系统的温度调节机制来平衡皮肤到目标温度。

Once the hydration and temperature of the skin has equilibrated (i.e., after 30 min) the skin surface temperature should be measured. The skin surface temperature should be within ±1° of the target temperature (32°) prior to applying the dosage form. The temperature of the receptor solution, or the circulating water bath, or the set point of a dry heat system, or any other component of the system should not be assumed to be the same as the skin surface temperature. Instead, the skin surface temperature should be directly measured (with an infrared thermometer or a thermocouple), and the thermoregulatory mechanism of the VDC system should be adjusted as needed to produce the target temperature of 32° at the skin surface. The stirrers can be run during the duration of the equilibration to speed up temperature stabilization.

一旦皮肤的水合作用和温度达到平衡(即30分钟后)，应测量皮肤表面温度。在施用剂型之前，皮肤表面温度应在目标温度(32°)的±1°内。受体溶液的温度，或循环水浴的温度，或干热系统的设定点，或系统的任何其他组成部分的温度不应假定与皮肤表面温度相同。而是直接测量皮肤表面温度(使用红外温度计或热电偶)，并根据需要调节VDC系统的热调节机制，使皮肤表面温度达到32°的目标温度。搅拌器可以在平衡期间运行，以加速温度稳定。

For specific dosing techniques to apply the product to the membrane, refer to In Vitro Permeation Test, Experimental Design, Dose.

将产品应用于膜的具体给药技术，请参见体外渗透试验，实验设计，剂量

One approach to sampling involves draining the receptor compartment of all the receptor solution and refilling it completely with fresh receptor solution. Removal of the entire receptor solution volume and full volume replacement of the receptor solution at each time point may provide optimal solubility sink conditions. Although the entire receptor solution volume is sampled, an aliquot is typically used for analysis. Another approach to sampling involves the removal of only a partial amount (i.e., an aliquot) of the entire receptor solution volume, leaving behind a partial volume of the receptor solution at each sampling. This approach can allow the concentration of a compound to increase above a quantification limit during time periods of low flux. However, the sampling of relatively small aliquots of the receptor solution for an IVPT study may introduce anomalous measurements of apparently negative flux in certain regions of the IVPT study and produce flux profiles that are difficult to interpret. Therefore, when sampling partial volumes, it is prudent to maximize the volume of the sample aliquot, in order to minimize the potential for apparent negative flux results.

取样的一种方法是抽干所有受体溶液的受体室，然后用新的受体溶液完全重新填充。在每个时间点去除整个受体溶液体积和全体积替换受体溶液可以提供最佳的溶解度条件。虽然整个受体溶液体积取样，但通常使用部分溶液进行分析。另一种取样方法涉及只去除整个受体溶液体积的一部分(部分取样)，在每次取样时留下部分体积的受体溶液。这种方法可以使化合物的浓度在低通量的时间段内增加到定量限制以上。然而，在IVPT研究中，相对小份额的受体溶液取样可能会在IVPT研究的某些区域引入明显负通量的异常测量，并产生难以解释的通量曲线。因此，在部分取样时，谨慎的做法是最大限度地增大样品的体积，以尽量减少出现明显负通量结果的可能性。

VDC systems should generally match the description of the equipment described in this chapter. Other designs can be used with sufficient scientific justification so long as they consist of a donor compartment separated from a receptor compartment by a membrane.

VDC系统一般应符合本章所述设备的描述。其他设计也可以有充分的科学依据，只要它们是由一层膜将供体隔室与受体隔室隔开的。

VDCs should be individually qualified and uniquely identifiable either by a manufacturer issued serial number or other means. The orifice area for the donor and receptor compartments can be determined using vernier calipers. Receptor compartment volume should be determined with all components (e.g., stir bars) in place. The receptor compartment volume should be determined (gravimetrically or volumetrically) to a precision of 0.01 mL. The nominal receptor compartment volume (e.g., 7 mL) should never be used in place of an accurately determined VDC volume (e.g., 6.89 mL). Using the nominal volume fails to account for variations of the receptor compartment volume due to manufacturing which could affect the accuracy and precision of test results.

VDC应逐个确认合格，并通过制造商颁发的序列号或其他方式唯一识别。供体和受体区室的孔口面积可以用游标卡尺确定。应在所有成分(如搅拌子)就位的情况下确定受体隔室体积。受体隔室体积的测定(重量法或体积法)精度为0.01 mL。标称受体隔室体积(如7 mL)绝不能代替准确测定的VDC体积(如6.89 mL)。使用标称体积不能解释由于制造差异而导致的受体隔室体积的变化，这可能会影响测试结果的准确性和精度。

All VDC systems should be properly maintained and requalified on a regular basis (as described previously). The relevant VDC systems (heating/thermoregulation, water bath and circulation tubes/manifolds, magnetic impeller/stirring, mechanical sampling, etc.) and other components of the VDC system should be kept clean and their operation should be evaluated to ensure that each diffusion cell can maintain the skin surface temperature within the target range (32 ± 1°), maintain the stirring speed within the specified range, and support the performance of the test within the specifications of the test method.

所有VDC系统都应定期进行适当维护和重新确认(如前所述)。相关VDC系统(加热/调温、水浴和循环管/歧管、磁力搅拌/搅拌、机械取样等)和VDC系统的其他部件应保持清洁，并对其运行进行评估，以确保每个扩散池能保持皮肤表面温度在目标范围内(32±1°)，保持搅拌速度在规定范围内。并支持在规定的测试方法范围内进行性能测试。

Any stirring device that is not stirring properly with the receptor solution present should be repaired or replaced. Since direct measurement of the stirring device used for testing is not always feasible, the stirring system (e.g., the rotating magnetic impeller) can be evaluated with a surrogate. For example, if stirring within a VDC is done with a 5 mm stir bar, the VDC can be temporarily removed, and a 25 mm stir bar can be placed in the cell block which can be measured to determine the stirring speed.

任何在受体溶液存在的情况下不能正确搅拌的搅拌装置都应修理或更换。由于用于测试的搅拌装置的直接测量并不总是可行的，因此搅拌系统(例如，磁力搅拌子)可以用替代品进行评估。例如，如果用5mm的搅拌棒进行VDC内的搅拌，则可以暂时移除VDC，并在单元块中放置25mm的搅拌棒，可以测量搅拌速度。

Sampling devices, such as pipettes, syringes, or automated systems should be evaluated to ensure that they are withdrawing and replacing sample volumes of the receptor solution with sufficient accuracy and precision.

应评估取样装置，如移液器、注射器或自动化系统，以确保它们以足够的准确性和精密度抽取和替换受体溶液的样品量。

Requalification of automated systems should be performed (e.g., every 6–12 months) based on considerations including the extent of equipment usage, the risk tolerance of the laboratory performing the test, and manufacturer’s recommendations. Requalification should also be performed if the system is relocated or undergoes a major repair. In situations where a new VDC unit is incorporated into a previously qualified VDC system (with a set of specific VDC units), the elements of VDC qualification relevant to the new VDC unit should be performed, and the elements of VDC qualification relevant to the (previously qualified) VDC system should be requalified, as relevant (e.g., this may include a requalification of the skin surface temperature control for the new/replacement VDC introduced into the previously qualified VDC system).

自动化系统的再确认应根据设备使用范围、实验室的风险承受能力和制造商的建议进行(例如，每6-12个月)。如果系统重新安置或进行大修，也应进行重新确认。在一个新VDC装入先前合格的VDC系统(与一组特定的VDC单位) 情况下,新VDC单位有关的VDC确认应该重新进行, 与(先前合格的)VDC系统相关的VDC资质要素应重新确认(例如，这可能包括对引入先前合格的VDC系统的新/替换VDC的表皮表面温度控制的重新确认)。)

The immersion cell system consists of the following components:

对于浸没池，USP装置2应根据溶解<711>中描述的程序进行鉴定。浸没池系统由以下部分组成:

 immersion cell which is an inert housing that holds a membrane and donor compartment.

浸没池是一种惰性外壳，可容纳膜和供体隔室。

An example immersion cell configuration can be seen in Figure 6 and Figure 7.

图6和图7中可以看到浸没池配置的示例。

The components of the immersion cell are listed in Figure 6. Formulation is placed in the sample compartment and sealed to prevent leaks by the membrane, washer, and retaining ring. The diameters of the orifices of the donor compartment, which define the dosage delivery surface area for the test, should be sized within ±5% of the specified diameter. The membrane should be held horizontal and faced up toward the paddle. Also, the membrane should be mounted so that it is flat, not wrinkled from overtightening the retaining ring. Donor compartments range from holding 300 mg to 4 g of the formulation; some models are adjustable.

浸没池的组件列在图6中。制剂放置在样品室并密封，用膜，垫圈，和固定环来防止泄漏。供体室的孔的直径，它定义了试验的剂量传递表面积，尺寸应在规定直径的±5%以内。膜应保持水平，面向桨。此外，膜应安装使其是平整的，避免过度拧紧扣环而起皱。供体室的装药范围从300 mg到4 g的制剂不等;有些型号是可调的。

The immersion cell can be used with a smaller version of USP Apparatus 2 (see á711ñ) with vessel volumes that vary from 50– 200 mL; however, the 150- or 200-mL vessels are more commonly used. A flat-bottom variation of the 150- or 200-mL vessel should be used to avoid the issue of dead space under the cell and standardize the orientation of the immersion cell in the vessel. Flat bottom vessels with a small peak at the base, to keep the immersion cell centered, may also be used.

浸没池可以与较小版本的USP Apparatus 2(见<711>)一起使用，容器体积从50 - 200毫升不等;然而，150或200毫升的容器更常用。应使用150或200毫升平地容器，以避免池体下底部不平坦的死区问题，并标准化浸泡池在容器中的方向。也可以使用底部有一个小峰的平底容器，以保持浸泡池的中心。

Use of the 150- or 200-mL vessel with USP Apparatus 2 requires the following modifications:

与USP装置2一起使用150或200毫升的容器需要进行以下修改:

• holders for the small-volume vessels (e.g., 200 mL vessels instead of standard 900-mL vessels)

•小容量溶出杯的支架(例如，200毫升容器而不是标准的900毫升容器)

• adapter plate to position the small-volume vessel in the center of the spindle

•小体积容器适配器板定位在主轴的中心

• smaller size shaft/paddle [2/3 cm (1/4 in)] to fit in the small-volume vessels

•更小尺寸的轴/桨[2/3厘米(1/4英寸)]，以适应小体积的容器

Immersion cell sample compartment volume should be set to a constant volume (compartment volume can be adjusted using an adjustment tool). Alignment of the retaining ring over the sample compartment is ensured using an alignment tool for the specific surface area of the immersion cell.

浸没池样品室体积应设置为恒定体积(室体积可使用调节工具进行调节)。使用浸没池的比表面积的对准工具确保样品室上的固定环的对准。

Observational checks should be performed prior to testing. The donor and receptor compartment orifices should be evaluated for any damage which may affect the orifice area. Damaged cells should not be used.

在测试之前应该进行观察性检查。应评估供体和受体腔室孔口是否有任何可能影响孔口面积的损伤。损坏的池不应使用。

Before loading the cells and placing the receptor solution in the vessel, set the paddle height, which is 10 ± 2 mm above the surface of the membrane. All other operational parameters, such as level, vibration, wobble, etc., should be set at the same conditions defined for USP Apparatus 2. The small-volume condition is qualified by first using the standard Apparatus 2 setup and Performance Verification Test, Apparatus 1 and 2 (see <711>).

在装载池体并将受体溶液放入容器之前，设置桨的高度，即膜表面以上10±2mm。所有其他操作参数，如液位、振动、摆动等，应设置在USP仪器2规定的相同条件下。通过首先使用标准装置2设置和性能验证测试，设备1和设备2(见<711>)来确定小容量条件。

Fill the reservoir dosage area with the sample under test. Ensure that the reservoir is filled to the top to minimize the possibility of air bubble formation between the surface of the sample and the membrane. A uniform surface can be obtained with the aid of a spatula. The typical quantity of sample is between 300 mg and 4 g, depending on the type of immersion cell used. Using forceps or tweezers, remove the membrane from the soaking receptor solution and place it over the top of the sample compartment by rolling it onto the surface to avoid entrapment of air. Ensure that the membrane is free of wrinkles. Assemble the immersion cell components as specified by the device manufacturer. Carefully place the completed assembly into the bottom of the dissolution vessel with the membrane facing up. The appropriate preheated receptor solution may be preloaded in the vessel or can be added after immersion of the immersion cell to start the test.

用待测样品填充储层上药区。确保药物充满到顶部，以尽量减少样品表面和膜之间形成气泡的可能性。借助于刮刀可以得到一个均匀的表面。样品的典型数量在300mg至4g之间，取决于所使用的浸没池的类型。使用镊子将膜从浸泡的受体溶液中取出，并将其滚动到样品室表面，以避免空气滞留。确保薄膜无褶皱。按照设备制造商的规定组装浸没池组件。小心地将完成的组件放入溶解容器的底部，使膜面朝上。适当的预热受体溶液可以预装在容器中，或者可以在浸泡池浸泡后加入，以开始测试。

At the end of the test period, dismantle the cell and examine the contents for anything unusual that could explain any anomalous data (e.g., leaks, bubbles, etc.).

在测试期结束时，拆卸池体并检查内容是否有任何异常，以解释任何异常数据(例如，泄漏，气泡等)。

Immersion cells should match the description of one of the instruments listed in this chapter. Other designs can be used with sufficient scientific justification so long as they consist of a donor compartment separated from a receptor compartment by a membrane.

浸没池应符合本章所列仪器的描述。其他设计也可以有充分的科学依据，只要它们是由一层膜将供体隔室与受体隔室隔开的。

At a minimum, the orifice area and donor compartments volume must be certified. Additional dimensions should also be certified when possible. Due to the uniformity in manufacturing immersion cells, individual identification of the cells and components is recommended, but not required.

至少，孔口面积和供体室体积必须经过认证。在可能的情况下，还应对其他尺寸进行认证。由于制造浸没池的一致性，建议对池体和组件进行单独确认，但这不是必需的。

Orifice area for the donor and receptor compartments can be determined using vernier calipers. Volume of the donor compartment can be calculated using the donor compartment diameter and height.

供体和受体区室的孔口面积可以用游标卡尺确定。供体隔室的体积可以用供体隔室的直径和高度来计算。

A known volume of receptor solution should be transferred to the vessel when testing by suitably accurate method or device. Immersion cells should only be used on suitably qualified dissolution apparatus.

当使用适当的精确方法或设备进行检测时，应将已知体积的受体溶液转移到容器中。浸没池只能在适当合格的溶出装置上使用

Requalification should be performed every 6–12 months, based on equipment usage, risk tolerance, and manufacturers recommendation. Requalification should also be performed if the system is relocated or undergoes a major repair.

应根据设备使用情况、风险承受能力和制造商建议，每6-12个月进行一次再确认。如果系统重新安置或进行大修，也应进行重新确认。

The components of the FDC are displayed in Figures 8–10. The skin is placed above the receptor compartment and kept in place by the donor compartment and a clamping mechanism. The skin should be held in a horizontal plane between the donor and receptor compartments. The donor and receptor compartments should be made out of an inert material. The surface area of the orifices of the donor compartment, which define the dosage delivery surface area for the test, should be sized within ±5% of the nominal value.

FDC的部件如图8-10所示。将皮肤置于受体隔室上方，并由供体隔室和夹紧机构保持在原位。皮肤应保持在供体和受体间室之间的水平面上。供体和受体隔室应由惰性材料制成。供体室的孔的表面积，它定义了试验的药物输送表面积，尺寸应该在标称值的±5%以内。

The FDC is connected to a pump which provides a constant or pulsation flow of receptor solution that passes through the receptor compartment, into a sample line then collected by a sample vial. Typically, the receptor compartment within the cell holds relatively small volumes (≤0.5 mL) as sink conditions are controlled, in part, by the flow rate of the pump. Flow rates in the range of 2–200 µL/min are common, however some methods may have flow rates in the thousands-of-microliters-per-minute range (i.e., in the milliliter-per-minute range), and the appropriate flow rate for each IVPT method may need to be optimized during method development depending upon the solubility of the drug in the receptor solution, the permeation rates during relevant sampling durations, and the limit of quantification of the receptor sample solution analysis method. The cells are typically placed on the arm of a fraction collector which will align the sample lines with vials or test tubes for each sample point. The FDC is heated to allow the membrane to be maintained at appropriate temperature.

        FDC连接到一个泵，该泵提供恒定或脉动流的受体溶液，通过受体室，进入样品管，然后由样品瓶收集。通常情况下，池体内的受体室容纳相对较小的体积(≤0.5 mL)，因为接收样品条件由泵的流速控制。流量在2-200µL/min很常见,但是一些方法可能在每分钟数千微升的流速范围(即每分钟毫升的范围内), 并且每种IVPT方法的适当流速可能需要在方法开发过程中根据药物在受体溶液中的溶解度、相关采样持续时间内的渗透速率以及受体样品溶液分析方法的定量极限来优化。池体通常放置在分馏收集器的臂上，分馏收集器将样品管线与每个样品点的小瓶或试管对齐。加热FDC以使膜保持在适当的温度。

Observational checks should be performed prior to testing. The donor and receptor compartment orifices should be evaluated for any damage which may affect the orifice area. Damaged cells should not be used.

在测试之前应该进行观察性检查。应评估供体和受体腔室孔口是否有任何可能影响孔口面积的损伤。损坏的池体不应使用。

Ideally, the skin should be gently stretched to ensure that it is flat (with no folds or wrinkles) when mounted upon the diffusion cell with the stratum corneum facing the air. An inert support membrane (e.g., a synthetic membrane validated for use with an IVRT method for the same drug product) may be used beneath the skin, as appropriate, as long as it does not impede the diffusion of the drug from the skin to the receptor solution. The donor compartment should then be installed on top of the skin ensuring that the skin is mounted securely in the diffusion cell. The receptor compartment may be filled with receptor solution either before or after mounting of the skin. Any bubbles underneath the skin should be removed by tipping the cell and/or facilitating the removal of the bubble via the outflowing receptor solution. The thermoregulatory mechanism of the FDC system should then be utilized to equilibrate the skin to the target skin surface temperature of 32°.

理想情况下，当角质层面向空气安装在扩散池上时，皮肤应该轻轻拉伸以确保它是平坦的(没有褶皱或皱纹)。只要不妨碍药物从皮肤向受体溶液的扩散，可酌情在皮肤下使用惰性支撑膜(例如，经IVRT方法验证可用于同一药品的合成膜)。然后应将供体隔室安装在皮肤的顶部，确保皮肤安全地安装在扩散池中。受体隔室可以在皮肤安装之前或之后充满受体溶液。皮肤下的任何气泡都应该通过倾斜池体和/或通过流出的受体溶液促进气泡的去除来去除。然后利用FDC系统的温度调节机制将皮肤平衡到32°的目标皮肤表面温度。

The FDC is connected to a pump and inflow as well as outflow tubing. When all the FDC for testing are connected to pumps, air bubbles may need to be purged from the receptor compartments. A typical method is the cells are tipped upward, with the outflow sample line raised, while the pump is run at a high speed which facilitates the removal of the air bubble from under the skin via the outflowing receptor solution. The pump can be stopped after all air has been purged from the receptor compartment. The cell should be lowered to the testing position and allowed to equilibrate.

FDC连接到泵、流入管和流出管。当所有用于测试的FDC都连接到泵上时，可能需要从受体隔间中清除气泡。一种典型的方法是将池体向上倾斜，使样品流出管升高，同时泵以高速运行，这有助于通过流出的受体溶液从皮肤下去除气泡。当所有空气从受体室中被清除后，泵就可以停止了。应将池体降低到测试位置并使其平衡。

Once the hydration and temperature of the skin has equilibrated (e.g., after 30 min) the skin surface temperature should be measured. The skin surface temperature should be within ±1° of the target temperature (32°) prior to applying the dosage form. The temperature of the receptor solution, or the circulating water bath, or the set point of a dry heat system, or any other component of the system should not be assumed to be the same as the skin surface temperature. Instead, the skin surface temperature should be directly measured (with an infrared thermometer or a thermocouple), and the thermoregulatory mechanism of the FDC system should be adjusted as needed to produce the target temperature of 32° at the skin surface.

一旦皮肤的水合作用和温度达到平衡(例如，30分钟后)，应测量皮肤表面温度。在施用剂型之前，皮肤表面温度应在目标温度(32°)的±1°内。受体溶液的温度，或循环水浴的温度，或干热系统的设定点，或系统的任何其他组成部分的温度不应假定与皮肤表面温度相同。相反，应直接测量皮肤表面温度(使用红外温度计或热电偶)，并根据需要调整FDC系统的温度调节机制，使皮肤表面温度达到32°的目标温度。

Collection vials or test tubes should be weighed when empty to determine the exact volume of sample present after collection has completed.

收集瓶或试管应在空时称重，以确定收集完成后样品的确切体积。

For specific dosing techniques to apply the product to the skin, refer to the In Vitro Permeation Test, Experimental Design, Dose. Set the pump to the flow rate to be used for testing and align the outflow sample tubes (which should all be the same length) with the first set of vials or test tubes.

有关将产品涂抹在皮肤上的具体剂量技术，请参阅体外渗透试验，实验设计，剂量。将泵设置为用于测试的流量，并将流出样管(应全部相同长度)与第一组小瓶或试管对齐。

After samples have been collected, the vials or test tubes should be weighed to determine the exact volume of receptor solution collected. This volume should be used when determining the total amount of drug present in each sample.

样品收集后，应称量小瓶或试管，以确定所收集受体溶液的确切体积。该体积用于测定每个样品中存在的药物总量。

FDC systems should generally match the description of the equipment described in this chapter. Other designs can be used with sufficient scientific justification so long as they consist of a donor compartment separated from a receptor compartment by the skin.

FDC系统一般应与本章所描述的设备描述相匹配。其他设计也可以有充分的科学依据，只要它们由皮肤将供体隔室与受体隔室分开。

FDCs should be individually qualified and uniquely identifiable either by a manufacturer issued serial number or other means. The orifice area for the donor and receptor compartments can be determined using vernier calipers. It may be appropriate to qualify the lengths of (inert) tubing for each of the flow-through diffusion cells, and their associated dead volumes, to accurately calculate the lag time before a sample elutes through the tubing and is collected.

FDCs应每个都确认合格，并通过制造商颁发的序列号或其他方式唯一识别。供体和受体区室的孔口面积可以用游标卡尺确定。为了准确地计算样品通过管道洗脱和收集之前的滞后时间，可以适当地限定每个流动扩散池(惰性)管的长度，以及它们相关的死体积。

The flow rate of the pump should be qualified for the rate used during testing. For flow rates in the microliters-per-minute range, it is recommended to extend the sampling time to reduce the effects of droplets adhering to the sample line. If an automated system is used it should be ensured that the sample lines are properly aligned over the vials.

泵的流量应符合试验时使用的流量。对于每分钟微升范围内的流速，建议延长采样时间，以减少液滴粘附在样品线上的影响。如果使用自动化系统，应确保样品管线在小瓶上正确对齐。

Skin surface temperature should be measured using an IR thermometer. The temperature of the heating block must be set higher than the desired membrane temperature (e.g., 33° for a 32° skin surface temperature).

皮肤表面温度应使用红外温度计测量。加热块的温度必须设置高于所需的膜温度(例如，对于32°的皮肤表面温度设为33°)。

All FDC systems should be properly maintained and requalified on a regular basis (as described previously). The relevant FDC systems (heating and thermoregulation, pumps, tubes, mechanical sampling systems, etc.) and other components of the FDC system should be kept clean and their operation should be evaluated to ensure that each diffusion cell can maintain the skin surface temperature within the target range of 32 ± 1°, maintain the flow rate within the specified range, and support the performance of the test within the specifications of the test method.

所有FDC系统应得到适当维护，并定期重新确认(如前所述)。相关的FDC系统(加热和温度调节、泵、管、机械取样系统等)和FDC系统的其他组件应保持清洁，并对其运行进行评估，以确保每个扩散池能够将皮肤表面温度保持在32±1°的目标范围内，将流量保持在规定的范围内，并在测试方法的规范范围内支持测试的性能。

The pump should be evaluated to ensure it is working properly. If a peristaltic pump is used, the tubing should be unclamped once the test has completed to prevent unnecessary wear on the tubing, which may cause variation in the flow rate. Peristaltic pump tubing should be replaced at regular intervals to ensure the flow rate remains consistent across all the cells. For automated sampling systems, sample tube alignment should also be checked to ensure that all samples are entirely collected into the vials or test tubes, without leakage, failure to capture samples, or sample loss for other reasons.

应对泵进行评估，以确保其正常工作。如果使用蠕动泵，测试完成后应松开泵管，以防止泵管不必要的磨损，这可能导致流量的变化。蠕动泵管应定期更换，以确保所有池体的流速保持一致。对于自动取样系统，还应检查样管对准，以确保所有样品完全收集到小瓶或试管中，无泄漏、样品捕获失败或因其他原因丢失样品。

Requalification of automated systems should be performed (e.g., every 6–12 months) based on considerations including the extent of equipment usage, the risk tolerance of the laboratory performing the test, and manufacturer’s recommendations. Requalification should also be performed if the system is relocated or undergoes a major repair. In situations where a new FDC unit is incorporated into a previously qualified FDC system (with a set of specific FDC units), the elements of FDC qualification relevant to the new FDC unit should be performed, and the elements of FDC qualification relevant to the (previously qualified) FDC system should be requalified, as relevant (e.g., this may include a requalification of the skin surface temperature control for the new/replacement FDC introduced into the previously qualified FDC system).

自动化系统的再确认应根据设备使用范围、实验室的风险承受能力和制造商的建议进行(例如，每6-12个月)。如果系统重新安置或进行大修，也应进行重新鉴定。如果一个新的FDC装置被合并到先前合格的FDC系统中(有一组特定的FDC装置)，则应执行与新FDC装置相关的FDC资格要素，并且与(先前合格的)FDC系统相关的FDC资格要素应重新确认(例如，这可能包括重新确认引入到先前合格的FDC系统中的新/替代FDC的皮肤表面)