**In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs**

ANDA申请中递交的外用药物产品体外释放（IVRT）研究

 Guidance for Industry

工业指南

*DRAFT GUIDANCE*

指南草案

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**本草案仅用于征求意见**

# ****Introduction****

# ****绪论****

This guidance is intended to assist applicants who are submitting abbreviated new drug applications (ANDAs) for liquid-based and/or other semisolid products applied to the skin, including integumentary and mucosal (e.g., vaginal) membranes, which are hereinafter called topical products.（注释2）Because of the complex route of delivery associated with these products, which are typically locally acting, and the potential complexity of certain formulations, topical products (other than topical solutions) are classified as complex products.（注释3）This guidance provides recommendations for in vitro release test (IVRT) studies that can be used to compare a proposed generic (test) topical product and its reference standard (RS) for the purpose of supporting a demonstration of bioequivalence (BE) to the reference listed drug (RLD). The reference standard 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），以下简称“外用制剂”（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）的体外释放试验（IVRT）研究提供建议，以论证与参比制剂（RLD）的生物等效性（BE）。参比制剂通常简称为RLD。（注释4）

Topical products in ANDAs within the scope of this guidance include ointments, creams, lotions, emulsions, pastes, shampoos, gels, suspensions, sprays, aerosols, foams, and other semisolid and/or liquid-based dosage forms dispensed with a structured arrangement of matter (which may include more than one phase state).

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、喷雾剂、气雾剂、泡沫剂foams、溶液和其他半固体和/或液体剂型，这些剂型具有特定的物质排列结构（可能包括多个相态）。

A complex product, as defined in the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023–2027 (GDUFA III Commitment Letter) (accessible at https://www.fda.gov/media/153631/download), includes, among others, products with complex formulations (e.g., colloids) and complex routes of delivery (e.g., locally acting drugs such as dermatological products).

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：胶体）和复杂递送途径（如：具体起效的皮肤用产品）的产品。

A reference listed drug “is the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA” (21 CFR 314.3(b)). A reference standard, which is selected by FDA, is the specific drug product that the ANDA applicant must use in conducting any in vivo bioequivalence testing required to support approval of its ANDA (see § 314.3(b)). We recommend that the reference standard also be used for in vitro testing. There may be circumstances (e.g., when the RLD is no longer marketed) in which the reference standard is a drug product other than the RLD. For more information on RLD and reference standard products, see the guidance for industry Referencing Approved Drug Products in ANDA Submissions (October 2020). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

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等效性研究中使用的对照药品”。推荐采用对照制剂（RS）进行体外试验。在有些情况下（如RLD已经退市），RS可以不是RLD。关于RLD和RS的更多信息，见“ANDA申请参照药品行业指南（2020年10月）”，我们会对指南定期进行更新，关于指南的最新版本，详见网址：https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

This guidance does not address drug products that are administered via ophthalmic, otic, nasal, inhalation, oral, or injection-based routes, or that are transdermal or topical 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、局部贴剂或缓释膜剂）。

It is beyond the scope of this guidance to discuss specific topical products to which this guidance applies. 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 conduct of IVRT studies that, in conjunction with other studies, as deemed necessary, may be appropriate to support a demonstration that a proposed generic topical product and its RLD are bioequivalent. FDA also recommends that applicants routinely refer to FDA’s guidance web pages, because additional guidances may become available 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IVRT研究的设计和实施时，查阅特定产品开发指南（PSGs）（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指南网站，及时获取最新的相关指南，以促进仿制药的开发。

In general, FDA’s guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidance 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，并且仅作为建议，除非当具体的法规或法令要求被引用时。在指南中用到的词语“应该”，是指建议，并非要求的意思。

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） program and 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。

The Federal Food, Drug, and Cosmetic Act (FD&C Act) generally requires an ANDA to contain, among other things, information to show that the proposed generic drug product 1) is the same as the RLD with respect to the active ingredient(s), conditions of use, route of administration, dosage form, strength, and labeling (with certain permissible differences) and 2) is bioequivalent to the RLD.（注释9）Thus, an ANDA will not be 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，具有相同的活性成分、使用条件、给药途径、剂型、规格和说明书（允许存在一些差异）；2）与RLD生物等效（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）

An IVRT study may be used to assess the rate of drug release (i.e., release of an active ingredient) from a topical product. Once validated, an IVRT study may also be useful in controlling product quality and/or establishing the acceptability of post-approval manufacturing changes. This guidance focuses on general considerations and recommendations for the method development, method validation, and conduct of IVRT studies that are submitted in ANDAs and intended to support a demonstration of BE.（注释11）

IVRT研究可用于评估外用制剂中药物的释放速率（即，活性成分的释放）。一旦经过验证，IVRT研究也可能有助于产品质量的控制和/或确定批准后生产变更的可接受性。本指南旨在说明，在ANDA申请中提交、拟用于BE论证的IVRT研究的方法开发和验证的一般考虑和建议。（注释11）

# ****IVRT Method Development****

# ****IVRT方法开发****

If an IVRT study is intended to support a demonstration of BE, the IVRT method development report should be submitted in the ANDA to show how the IVRT method was optimized, and to support a demonstration that the method parameters selected for the IVRT are appropriate or necessary, particularly in situations where the method parameters are different from the methods recommended in this guidance and described in the United States Pharmacopeia (USP) General Chapter <1724>.（注释12）The Agency’s interest in reviewing the method development report is to understand why specific IVRT method parameters were selected and whether they are suitably sensitive and reproducible. This method development report should clearly indicate/distinguish the method parameters used for each set of data, illustrate the efforts made to optimize the IVRT method, and demonstrate that the method parameters selected for the IVRT are appropriate.

如果拟采用IVRT研究支持BE论证，在ANDA申请中，应递交IVRT方法开发报告，说明IVRT方法是如何优化的，并提供证据说明所选的IVRT方法参数是合理的或必要的，尤其是所选的方法参数与本指南和USP<1724>中推荐或描述的参数不一致时（注释12）。监管机构在审核方法开发报告时，比较关注IVRT方法参数选择的合理性，以及它们是否具有合适的灵敏度和重现性。应在方法开发报告中清楚的说明每组数据对应的方法参数，阐述优化IVRT方法所做的努力，证明所选的方法参数是合适的。

Applicants are encouraged to use the recommendations in this guidance, and if an applicant elects to use methods that are different from those recommended in this guidance, the IVRT method development report should demonstrate why it is scientifically justified to use an alternative approach than what is recommended in this guidance or USP<1724>to optimize the IVRT method.（注释13） Specific examples of procedures are described in subsequent sections, to help applicants identify circumstances when information should be submitted in the ANDA to explain why an alternative procedure was utilized.

鼓励申请人采用本指南中推荐的方法，如果申请人采用本指南推荐外的其它方法，则应在IVRT方法开发报告中说明选择替代方法，而未采用本指南或USP<1724>中推荐的方法，进行IVRT方法优化的科学合理性。（注释13：同上）后面的章节提供了具体的示例描述，用于帮助申请人确认ANDA申请中需要递交的信息，解释为什么采用了替代的方法。

The IVRT method development studies, being exploratory in nature, are often performed using a sample analytical method that is not validated (e.g., a high-performance liquid chromatography (HPLC) or ultrahigh performance liquid chromatography (UPLC) method); also, IVRT method development studies are often conducted in a manner that is not compatible with a quality management system which would otherwise make the evidence generated suitable to support valid conclusions. Such method development studies would not be suitable to demonstrate the validity of an IVRT method, or the associated results. Therefore, although it may appear to be redundant, certain experiments performed during IVRT method development may need to be repeated during IVRT method validation, using appropriate controls, like a validated analytical method and procedures that are compatible with a suitable quality management system.

IVRT方法开发研究具有探索性研究的属性，通常是采用未经验证的样品分析方法[如，HPLC（高效液相色谱法）或UPLC（超高效液相色谱法）]进行的；此外，IVRT方法开发研究通常在不符合质量管理系统的环境下进行的，所产生的证据（或结果）不足以支撑结论的可靠性。这种方法开发研究不适于证明IVRT方法或相关结果的有效性。因此，尽管看起来似乎是多余的，但在IVRT方法开发期间进行某些试验可能需要在IVRT方法验证期间重复进行考察，进行适当的控制，如与适当的质量管理体系相兼容的已验证的分析方法和程序。

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

需要注意的是，应将IVRT方法开发和IVRT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IVRT结果，所有相关的方法参数和试验条件/对照都应保持一致，这点非常重要。当采用不同的方法参数可以获得明显相似的试验结果时，应在方法开发报告中清楚的说明。在方法开发报告中，也应阐明扩散池是平行还是单独运行（如，在不同的日期）的。此外，应说明在IVRT试验中，用于样品分析的具体方法（如，HPLC或UPLC方法），并说明分析方法是否经过了验证（在样品分析时或样品分析后）。

## ****IVRT Method Parameters****

## ****IVRT方法参数****

Theoretical or empirical information should be provided to explain the selection of IVRT method parameters such as the equipment, product dose amount, sampling times, stirring/agitation rate, etc. When the equipment selected is among the models of equipment in the USP<1724>, Semisolid Drug Products – Performance Tests, and when the product dose amount or stirring rate is a parameter that is fixed (not adjustable) with the selected equipment, it may be sufficient to explain these facts.

应提供理论或经验信息来解释IVRT方法参数的选择，如设备、上样量、取样时间、搅拌速率等。当选择的设备是USP<1724>半固体药物制剂—性能测试 中所述设备时，且上样量或搅拌速率与所选的设备匹配（未调节），可充分解释选择的合理性。

It is unconventional for IVRT sampling times to be selected within a study duration of less than 4 hours. This may occur in situations where the fixed product dose was depleted to such a great extent by 4 hours that the release kinetics were no longer linear thereafter (when plotted vs. the square root of time). In such instances, it would be appropriate to explain the efforts that were made to optimize the IVRT method (e.g., using a different diffusion cell equipment that allowed for a larger product dose to be used) so that the sustained steady state release kinetics could potentially be characterized over a conventional IVRT duration of 4 to 6 hours.

通常情况下，所选的IVPT取样时长不应少于4小时。但是，对于某些特定类型的制剂，如果在大于4小时后，因产品剂量消耗非常大，之后的时间点不能呈线性关系（以释放量对时间的平方根作图）。在这种情况下，应该阐述为优化IVRT方法所做的努力（例如，使用不同的扩散池设备，以便可以采用更大的产品上样量），确保在4～6小时内呈现持续稳态释放动力学。

## ****IVRT Receptor Solution****

## ****IVRT接收介质****

It is conventional to evaluate different receptor solutions during IVRT method development (all using the same membrane that has broad chemical compatibility with the receptor solutions evaluated); these receptor solutions are frequently binary hydro-alcoholic mixtures selected based upon the solubility and stability of the (frequently hydrophobic) drug in the receptor solution. The receptor solutions are conventionally sampled at least hourly across a 6-hour duration.

通常，需要在IVRT方法开发过程中对不同的接收介质进行评估（采用与待评估的接收液具有化学兼容性的同一种膜）；根据药物（通常是疏水性的）在接收液中的溶解性和稳定性，接收介质通常是水-醇二元混合体系。接收液取样频率通常是在6个小时的研究中，每小时至少取样一次。

Information on the empirical solubility and stability of the drug in the receptor solution, as well as information on the linearity and precision of the resulting drug release rate in an IVRT should be provided to help explain the selection of a receptor solution for the test method. The linearity of the drug release rate (slope) across all time points should ideally have an r2 value of ≥ 0.97. In situations where the solubility of the drug in the receptor solution limits the release kinetics, causing a reduction in the release rate at the last time point(s), it may be appropriate to evaluate different receptor solutions. It may be appropriate to truncate the IVRT method to a 4- or 5-hour sampling duration if the linearity of the release rate in that truncated duration is improved (exhibiting a higher r2 value), and if other aspects of the release kinetics (e.g., precision) in that receptor solution are optimized compared to other receptor solutions evaluated.

应提供药物在接收液的溶解度和稳定性信息，以及在IVRT研究中获得的药物释放速率的线性和精密度结果，用于解释IVRT方法研究中接收液选择的合理性。理想情况下，各时间点的药物释放速率（斜率）应呈线性关系（r2≥0.97）。如果药物在接收液中的溶解度限制了释放动力学，导致最后的时间点药物释放速率降低，此时应对不同的接收介质进行评估。但是，如果较短的时间，释放速率的线性得到改善（显示出更高的r2值），且该接收液释放动力学的其他方面（例如，精密度）与评估的其他接收液相比得到优化，那么将IVRT方法缩短为4小时或5小时可能是合适的。

One advantage of selecting an optimal receptor solution as an initial step in IVRT method development is that it allows for the sample analysis method to be optimized for the selected receptor solution sample matrix before proceeding to an evaluation of different membranes using that receptor solution.

选择最佳接收液作为IVRT方法开发初始步骤的一个优点是，在使用接收液对不同膜评估前，可先采用选定的接收液对样品分析方法进行优化。

## ****IVRT Membrane****

## ****IVRT膜****

It is conventional to evaluate different membranes during IVRT method development (all using the same receptor solution); these membranes are frequently synthetic membranes used for the filtration of particulate matter in solutions. IVRT membranes are selected based upon their effective pore size (e.g., 0.45 micrometers (μm)), as well as their expected inertness to binding the drug. Information should be provided in the IVRT method development report on each membrane’s binding to the drug and its chemical compatibility with relevant receptor solution(s) selected for the IVRT method (based on the preceding phase of IVRT method development), as well as information on the linearity and precision of the resulting release rate when each membrane is used in an IVRT, as this information can help to explain why a specific membrane is optimal for the IVRT method.

一般情况下，在IVRT方法开发中，（使用相同的接收介质）对不同的膜进行评估；通常采用合成膜过滤溶液中的微粒物质。在IVRT膜的选择中，可根据膜的有效孔径（如0.45μm），以及它们对药物的预期惰性。应在IVRT方法开发报告中，提供每种膜对化合物结合的信息和膜本身对IVRT方法中所选接收液的惰性（根据IVRT方法开发的前一阶段），以及在IVRT中所用的每种膜的药物释放线性和精密度信息，这些信息有助于解释IVRT方法中膜选择的合理性。

# ****IVRT Method Validation****

# ****IVRT方法验证****

The equipment, methodologies, and study conditions used in the IVRT pivotal study should be appropriately validated or qualified. It is conventional to initiate the validation of the sample analytical method (e.g., a HPLC or UPLC method) for the IVRT before initiating the IVRT method validation itself, although certain components of the sample analysis method validation (e.g., stability) often proceed in parallel with the IVRT method validation. If an applicant elects to use equipment, methodologies, or study conditions that are different from those recommended in this guidance or in USP<1724>, the applicant should demonstrate why the differences are scientifically justified.（注释14） It is important to consistently identify all relevant method parameters for each set of IVRT results, making it clear that the results were obtained using the same IVRT method parameters, and clarifying which sets of diffusion cells were run in parallel or separately. Detailed protocols and well-controlled test procedures are recommended to ensure the precise control of dosing, sampling, and other IVRT study parameters, and of potential sources of experimental bias.

应对IVRT正式研究中所用的设备、方法和研究条件进行合理的验证或确认。通常，在进行IVRT方法验证前，首先进行样品分析方法验证（如HPLC或UPLC方法），尽管在样品分析方法验证中的某些试验（如稳定性）与IVRT方法验证是平行进行的。如果未采用本指南或USP<1724>中推荐的设备、方法或研究条件，申请人应证明其科学合理性。（注释14）需要强调的是，要一致地识别每组IVRT结果的所有相关方法参数，明确使用相同的IVRT方法参数获得的结果，并阐明扩散池是平行运行的或单独运行的。推荐建立详细的方案和良好的控制试验程序，以确保精确控制上样、取样和其他IVRT研究参数，以及潜在的实验偏差来源。

The qualification of an IVRT method parameter refers to the process of defining what attributes make it suitable to perform its function in the IVRT method. For example, when hourly measurements of the temperature at the membrane surface (when mounted in a diffusion cell) demonstrate that an IVRT equipment can maintain a membrane surface temperature in the range of 32°C ± 1°C across 6 hours, the results can support a demonstration that the equipment is qualified to perform its function in an IVRT method for which a method parameter is the control of membrane surface temperature in the range of 32°C ± 1°C across 6 hours. While an IVRT membrane surface temperature in the range of range of 32°C ± 1°C is appropriate for topical products applied on the skin, for topical products applied on mucosal membranes (e.g., a vaginal gel) the relevant IVRT membrane surface temperature would be 37°C ± 1°C. The validation of the IVRT method should incorporate the following qualifications and controls, performed using validated sample analytical procedures, as applicable.

IVRT方法参数确认是表征其属性适合在IVRT方法中执行其功能的过程。例如，当将（合成）膜安装在扩散池中，（待膜表面温度稳定后）每小时测定膜表面温度一次，结果IVRT设备能在6小时内保持膜表面温度在32°C ± 1°C范围内，这个结果可用于证明，该设备可用于执行其功能，IVRT方法参数可以在6小时内控制膜表面温度在32°C ± 1°C范围内。32°C ± 1°C的膜表面温度适用于皮肤外用制剂，而粘膜外用制剂（如阴道用凝胶）的相关膜表面温度为37°C ± 1°C。如适用，采用已验证样品分析方法，在IVRT方法验证进行以下确认和控制。

## ****Equipment Qualification****

## ****设备确认****

Suitable equipment for the IVRT method are described in USP General Chapter<1724>. These include different models of a vertical diffusion cell and an immersion cell. Other models of vertical diffusion cells and immersion cells that are essentially the same in design and/or operational principles as those described in USP General Chapter<1724>may also be suitable.

在USP<1724>中有可用于IVRT方法的相应设备描述，包括不同模型的立式扩散池和一种的浸没池。与USP<1724>中描述的立式扩散池和浸没池具有相同的设计和/或操作原理的其他设备，也可以使用。

The operating principles and specific test procedures differ among the various equipment; relevant procedures from the manufacturer may be used for installation, operation, 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 membrane is mounte; (2) the empirically measured volume of the receptor solution compartment/vessel for each diffusion cell; (3) the stability of the temperature measured at the membrane surface (e.g., at 32°C ± 1°C), or just below the membrane, across a relevant duration (e.g., 6 hours); and (4) the rate of stirring or agitation, as applicable.

每种设备的操作原理和特定测试方法均不相同；可根据生产商提供的相关规程进行安装、操作和性能确认。每个扩散池的实验室确认内容，至少应包括：1）测定供给室和接收室之间膜安装位置的孔口扩散面积；2）测量每个接收室的容积；3）在相关研究期间（如，6小时），测定膜表面或膜下温度（如，32℃±1℃）的稳定性；和4）如适用，测定搅拌速率。

If information related to the diffusional area of the orifice and the volume of the receptor solution compartment for each diffusion cell is available from the manufacturer, that information should be provided for each relevant diffusion cell, in addition to the empirical measurements made by the laboratory. The equipment should control the diffusion cell thermoregulation so that the membrane surface temperature is verified to be stable (e.g., at 32°C ± 1°C) for each diffusion cell (e.g., measured by a calibrated infrared thermometer) before dosing. If it is not feasible to verify that the membrane surface temperature of a diffusion cell has equilibrated and stabilized (e.g., at 32°C ± 1°C) before dosing because of design and operating principles of a specific equipment, the qualification of that equipment should demonstrate that, under the specific conditions used for the IVRT method, the membrane surface temperature can be expected to be stable (e.g., at 32°C ± 1°C) for each diffusion cell throughout the test.

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研究时测定的相关结果，还应提供生产商提供的信息。设备应可以控制扩散池的温度调节，确保在上样前，每个扩散中膜表面温度稳定（例如，通过校准的红外温度计测定在32℃±1℃范围内）。如果由于设备的特定设计和操作原理，在上样前无法确认扩散池的膜表面温度已经平衡和稳定（例如，在32℃±1℃），对于这种类型的设备确认应证明，在IVRT方法特定条件下的整个测试过程中，每个扩散细胞的膜表面温度可以预期保持稳定（例如，在32℃±1℃）。

## ****Membrane Qualification****

## ****膜确认****

Membrane inertness should be evaluated in relation to membrane binding of the drug in the receptor solution at a concentration relevant to the range of drug concentrations in the receptor solution during the test. Determinations should be based upon a minimum of three replicate membrane incubations for the IVRT duration at the relevant temperature (e.g., 6 hours at 32°C ± 1°C). Three replicate control incubations should be performed in parallel, without membranes, to monitor for drug loss that is not associated with membrane binding. Aliquots of these solutions should be collected before and after the duration of incubation, to assess any decrease in the amount of drug in solution. The recovery of drug in solution is recommended to be within the range of 100% ± 5% at the end of the test duration to qualify the inertness of the membrane.

在实验期间，接收液中药物浓度的范围内，通过评估膜对接收液中药物的吸附作用，论证膜的惰性。在IVRT研究的整个期间，将膜放置到相关温度的接收液中进行孵化（例如，在32℃±1℃条件下放置6小时），至少重复测定三份。并在相同条件下，同步考察至少三份不加膜时，与膜吸附无关的药物损失。在孵化前后分别收集相同量的接收液，以评估溶液中药物的降低。如果实验结束时，溶液中药物的回收率在100% ± 5%，可认为在该条件下膜是惰性的。

## ****Receptor Solution Qualification****

## ****接收介质确认****

The reason for selecting the composition of the receptor solution used for the IVRT study should be explained. The solubility of the drug in the IVRT receptor solution should be empirically determined in triplicate, to illustrate that the solubility of the drug in the receptor solution exceeds the highest sample concentration in the IVRT pivotal 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 the relatively higher release rate of a formulation that is 150% of the nominal strength of the RS during the IVRT method validation).

应解释在IVRT研究中选择接收介质组成的理由。药物在接收介质中的溶解度，应进行三次重复检测经验确定，以说明药物在接收介质中的溶解度超过IVRT正式研究中药物的最大浓度，理想值应该是一个数量级或者是足以确切促成研究期间释放速率的线性关系（即使在IVRT方法验证期间评估相对较高的释放率，即RS的标称规格的150%）。

## ****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 appropriately qualified. Evidence to qualify a sampling procedure should illustrate that the sampling technique can reliably collect a consistent volume of the sample from the well-mixed volume of the receptor compartment at each sampling event, and that no artifacts are likely to be created by the sampling technique (e.g., because of carryover between samples in automated sampling systems or because of sampling from an unmixed volume in the sampling arm of a vertical diffusion cell). Information should be included describing the equipment manufacturer’s specification for the accuracy and precision of receptor solution sampling, when available.

应对每个时间点接收液取样的准确性和精密度进行确认。在取样程序的确认过程中应证明，所用取样技术可以从混合良好的接收室中始终一致的收集到相同体积的接收液，且不会因取样技术的原因引起误差（例如，由于自动取样系统中样品间的相互干扰或样品的残留，或因为从混合不均一的立式扩散池采样臂中取样）。如适用，应描述设备生产商关于接收液取样准确度和精密度的规范信息。

## ****Environmental Control****

## ****环境控制****

Ambient laboratory temperature and humidity during the study should be monitored and reported. An environmentally controlled temperature range of 21°C ± 2°C is recommended, and, if feasible, a humidity range of 50% ± 20% relative humidity is recommended.

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±20%RH之间。

## ****Linearity and Range****

## ****线性和范围****

The linearity (r2 value) of the release rate (slope) should be plotted across the range of the sampling times, which corresponds to the IVRT study duration. The linearity of drug release should be calculated and reported for each diffusion cell and compared within and across all IVRT runs. For the release rate to be considered suitably linear, it should have an r2 value ≥ 0.97 across the recommended IVRT study duration of 4–6 hours. An IVRT study duration of less than 4 hours may be insufficient to assess whether the release rates being compared for the test topical product and RS represent their steady state drug release kinetics, but an IVRT study duration of less than 4 hours (which is not recommended) may be justified if supported by compelling experimental data within the method development report to illustrate that reasonable and scientifically appropriate efforts were made to optimize the IVRT method. The IVRT method linearity and range should be established based upon the results of the precision and reproducibility runs, described further below.

在IVRT的整个研究期间，根据所有采样时间点的释放速率绘制标准曲线，应呈线性关系（r2值）。应计算和报告每个扩散池的药物释放线性方程，并与IVRT研究其它结果进行比较。释放速率呈现合适线性关系的评价指标是，在推荐的4～6小时IVRT研究期间，r2值应≥0.97。通常情况下，小于4小时的IVRT研究时长不足以评估，用于自研制剂和RS比较的释放速率是否代表其稳态药物释放动力学，但是，如果方法开发报告中有令人信服的实验数据支持，可以说明在优化IVRT方法时，做出了合理和科学的努力，低于4小时的研究时长（不推荐）也是可以接受的。IVRT方法的线性和范围应建立在精密度和重复性试验结果的基础上，详见下文。

## ****Precision and Reproducibility****

## ****精密度和重现性****

The intra-run and inter-run precision and reproducibility may be compared for the release rate (slopes) calculated for each diffusion cell. The mean, standard deviation, and percent coefficient of variation (%CV) among slopes may be calculated within and across all runs, and a minimum intra-run and inter-run %CV≤15% is recommended. Runs may be organized to facilitate a simultaneous evaluation of intra/inter-instrumentation and/or intra/inter-operator precision and reproducibility. A minimum of three independent precision and reproducibility runs is recommended.

可根据每个扩散池的释放速率（斜率）计算批内精密度和批间重现性。应计算并报告所有批内和批间斜率的均值、标准偏差和变异系数（%CV），批内和批间的变异系数（%CV）均应小于等于15%。批的运行应便于仪器内/间 和/或 操作者内/间的精密度和重现性的同时评估。建议至少进行三次精密度和重现性试验。

## ****Dose Depletion****

## ****剂量消耗****

The recovery of released drug in the receptor solution should be characterized in each diffusion cell as the cumulative amount of drug released into the receptor solution over the IVRT study duration. This may be expressed as a percentage of the amount of drug in the applied dose (which may be estimated based upon the nominal strength of the drug in the topical product and the approximate mass of topical product dosed on the membrane). For example, if 1 gram (g) of a topical product containing 5% drug was dosed on the membrane of each diffusion cell, the amount of drug in the applied dose may be estimated to be 50 mg. If a total of 10 mg of drug diffused into the receptor solution of each diffusion cell across the 6-hour duration of the IVRT, it would be possible to estimate that the 50 mg dose would have been depleted by 10 mg, amounting to a 20% dose depletion. The average percentage dose depletion may thereby be estimated and should be reported. While steady state release kinetics can typically be assumed under conditions when the dose depletion is less than 30%, for some topical products, steady state release kinetics may continue to be observed at higher percentage dose depletions. The IVRT method may be considered adequate despite a dose depletion of greater than 30% when experimental evidence illustrates that the release rate (slope) remains suitably linear for each diffusion cell when plotted versus the square root of time.

应计算每个扩散池接收液中释放药物的回收率，用于表征在IVRT的整个研究期间，接收液中药物释放的累积量，这可以表达为上样剂量中药物（根据外用制剂中药物的标示规格，以及膜上的大致上样量进行估算）的百分含量。例如，如果扩散池中膜上的上样量为1g、制剂的标示规格为5%，则上样剂量中活性物质的量约为50mg。如果在IVRT 6小时的研究中，接收液中药物扩散的总量为10mg，可以估算50mg活性物质的消耗量为10mg，则剂量消耗为20%。应计算和报告平均剂量百分比。通常，稳态释放动力学应假定剂量消耗低于30%，但是，一些外用制剂，在剂量消耗大于30%时，也能持续观察到稳态释放动力学。对于消耗量大于30%的IVRT方法，如果试验结果表明，当以释放量对时间的平方根作图时，每个扩散池的释放速率也能保持线性关系，这种方法也可以考虑是充分的。

**Discrimination Sensitivity, Specificity, and Selectivity**

## ****区分力—灵敏度、专属性和选择性****

The IVRT method should be able to discriminate drug release rates from similar formulations. This should be evaluated by comparing the release rate from the test formulation with that from two comparable formulations in which the concentration of drug has been altered – one with a higher strength (150% of the nominal concentration of the RS) and one with a lower strength (50% of the nominal concentration of the RS). If precipitation of the active ingredient is observed when formulating a topical product at 150% compared to the nominal strength, it may be necessary to use different strategies, which may be discussed with the Agency before the submission of an ANDA during a pre-ANDA product development meeting（注释15） or via a controlled correspondence.（注释16） The composition and procedures for preparation of these higher and lower strength formulations should be reported, although these formulations need not be prepared in a manner compatible with current Good Manufacturing Practices. The discrimination ability of the IVRT method should be described using three concepts of discrimination ability: sensitivity, specificity, and selectivity.

IVRT方法应能区分相似配方制剂的药物释放速率。这可以通过将受试配方制剂的释放速率与另外两个改变规格的配方制剂的释放速率进行对比来评估，即：一个较高规格（RS标示规格的150%）和一个较低规格（RS标示规格的50%）。如果与标示规格相比，150%规格的配方制剂中活性成分会析出，可以在ANDA递交前的产品开发会议上（注释15）与FDA就该问题进行讨论，或通过受控信函（注释16）与FDA沟通。尽管这些配方制剂不是在符合cGMP要求的条件下制备，也应报告较高和较低规格配方制剂的组成和制备方法。可以采用以下三个概念描述IVRT方法的区分力：灵敏度、专属性和选择性。

### *IVRT Sensitivity*

### *IVRT灵敏度*

IVRT sensitivity is the ability to detect changes in the release rate, as a function of drug concentration in the formulation. If the IVRT method consistently identifies higher or lower rates of release for test formulations with increased or decreased drug concentrations, respectively, relative to the formulation at the nominal strength of the RS run in parallel on the same day, the IVRT method would generally be considered sensitive.

IVRT灵敏度是检测释放速率变化的能力，其中，释放速率为配方制剂中药物浓度的函数。如果在相同的日期，对RS、较高规格和较低规格的配方制剂进行平行研究，相对于RS，较高规格或较低规格的配方制剂能分别呈现出较高或较低释放速率，则认为IVRT方法是灵敏的。

### *IVRT Specificity*

### *IVRT专属性*

IVRT specificity is the ability to accurately monitor the proportionality of changes in the release rate as a function of drug concentration in the formulation. This proportionality may be illustrated in a plot of the relationship between the formulation concentration and the average IVRT release rate (slope). The specificity of the IVRT method should be calculated, plotted with a linear trendline, and the linearity quantified and reported as an r2 value. To be considered suitably specific, an IVRT method should be proportionally linear in its response to differences in release rates, with a minimum r2 value ≥ 0.95 for the correlation of the formulation concentration to the average IVRT release rate (slope).

IVRT专属性是准确监控释放速率变化比例的能力，其中，释放速率为配方制剂中药物浓度的函数。这种比例可以用配方浓度与IVRT平均释放速率（斜率）之间的关系图来说明。通过绘制线性趋势线，量化并报告r2值，来评估IVRT的专属性。IVRT方法对释放速率的响应按线性应呈比例关系，如果配方浓度与IVRT平均释放速率（斜率）的线性相关性r2值≥0.95，则认为该方法具有合适的专属性。

IVRT specificity is a function of the proportionality of release rates across different strengths of the product, some, or all of which may be formulated as small-scale laboratory batches, with each strength having a slightly different formulation composition to accommodate for the different amount of the active ingredient in that strength of the product. These slight formulation differences across the different strengths of the product may impact the ideal proportionality of release rates across the different strengths of the product.

IVRT专属性是不同规格制剂产品释放速率变换比例的函数，其中一些或可能所有配方制剂均是小批量实验室批次，每种规格的配方成分略有不同，以适应不同规格产品中活性成分的不同含量。这种不同规格制剂产品配方的轻微变化可能影响不同规格制剂产品释放速率的理想变化比例。

Thus, the proportional linearity of release rates across different strengths of the product may be impacted by formulation differences across the strengths that are independent of the proportional responsiveness of the IVRT method. The minimum r2 value ≥ 0.95 for the correlation of the formulation concentration to the average IVRT release rate (slope) takes into account that the IVRT method’s response to differences in release rates may not appear to be perfectly proportional because of formulation differences that are independent of the IVRT method.

因此，不同规格产品释放率的比例线性可能受到不同规格配方差异的影响，而这些差异与IVRT方法的比例响应性无关。因配方差异与IVRT方法无关，且考虑到IVRT方法对释放速率差异的响应可能不是完全成比例的，因此，要求配方浓度与IVRT平均释放率（斜率）相关性的最小r2值≥0.95。

Note that the linearity of release rates across different strengths of the product (which assesses the specificity of the IVRT method, with a minimum r2 value ≥ 0.95) is fundamentally different and has different scientific considerations than the linearity of the release rate for a single strength of the product across the range of the sampling times (which assesses the IVRT method’s ability to monitor the steady state release kinetics of the active ingredient, with a minimum r2 value ≥ 0.97). Despite the potential for different scientific considerations to impact the linearity of the IVRT results in each context, for well-developed and suitably controlled IVRT methods, the r2 value ≥ 0.99 is routinely observed in both contexts.

需要注意的是，产品不同规格释放速率的线性关系（评估IVRT方法的专属性，要求r2≥0.95）与同一规格产品在不同采样时间点获得的释放速率线性关系（评估IVRT方法监控活性成分稳态释放动力学的能力，要求r2≥0.97）具有根本不同的科学考虑。尽管基于不同的科学考虑因素，可能会影响IVRT结果的线性关系，但对于经过良好的开发和适当控制的IVRT方法，在两者的背景下，通常都能满足r2≥0.99的要求。

### *IVRT Selectivity*

### *IVRT选择性*

IVRT selectivity is the ability of the IVRT method to discriminate the drug release rates between the reference topical product and the altered (50% and 150% nominal strength) concentration test formulations such that their release rates are determined to be statistically inequivalent compared to that from the nominal reference strength formulation. Determination of inequivalence between release rates should be evaluated using the statistical approach described in USP General Chapter<1724>.

IVRT选择性是指IVRT方法区分对照外用制剂和改变规格的配方制剂（50%和150%规格）之间，释放速率差异的能力，应证明改变配方制剂规格后，其释放速率与对照外用制剂相比，在统计学上不等效。可以根据USP<1724>中描述的统计学方法，对释放速率的不等效性进行评估。

Specifically, the release rates from six cells dosed with the nominal reference strength formulation should be compared with the release rates from 6 cells dosed with the formulation at 150% the nominal reference strength, using the statistical approach described in USP General Chapter<1724>. All 12 cells being compared should have been run in parallel on the same day, and the release rate from the formulation at 150% the nominal reference strength should fail to show equivalence to the release rate from the nominal reference strength formulation.

具体来说，将对照标示规格制剂（即100%规格）和150%规格配方制剂各6杯的释放速率，按USP<1724>中描述的统计学方法进行比较。所有12杯应在同一天平行运行，150%规格配方制剂的释放速率应与对照制剂的释放速率不等效。

The release rates from 6 cells dosed with the nominal reference strength formulation should also be compared with the release rates from 6 cells dosed with the formulation at 50% the nominal reference strength, using the statistical approach described in USP General Chapter<1724>. All 12 cells being compared should have been run in parallel on the same day, and the release rate from the formulation at 50% the nominal reference strength should fail to show equivalence to the release rate from the nominal reference strength formulation.

将对照标示规格制剂（即100%规格）和50%规格配方制剂各6杯的释放速率，按USP<1724>中描述的统计学方法进行比较。所有12杯应在同一天平行运行，50%规格配方制剂的释放速率应与对照制剂的释放速率不等效。

### *IVRT Supplemental Selectivity*

### *IVRT补充选择性*

IVRT supplemental selectivity is the ability of the IVRT method to discriminate the drug release rates between the reference topical product and an altered formulation with the same nominal reference strength, such that their release rates are determined to be statistically inequivalent.

IVRT补充选择性是IVRT方法区分对照外用制剂和具有相同规格、不同配方的制剂之间，释放速率差异的能力，应证明它们的释放速率在统计学上不等效。

The demonstration of IVRT selectivity (distinct from supplemental selectivity) validates the ability of the IVRT method to discriminate differences in release rates under conditions when the release rate is expected to differ in a predictable manner (i.e., when there are different concentrations of drug in the formulation).

IVRT选择性论证（不同于补充选择性）是确认IVRT方法区分不同释放速率的能力，该释放速率经预测会存在不同（即，配方制剂中具有不同浓度的药物）。

A separate and supplemental demonstration of the selectivity of an IVRT method, when feasible, independently validates the ability of the IVRT method to discriminate differences in release rates under the conditions of the pivotal IVRT study, in which the test and reference topical products are compared at the same strength. Thus, the supplemental demonstration of the selectivity of the IVRT method validates that it can detect differences in the release rate that are associated with aspects of the formulation other than the strength, and this is ideal, when feasible.

对IVRT方法选择性的补充论证而言，在可行的情况下，在IVRT正式研究中，采用相同规格的自研制剂和对照外用制剂，单独确认IVRT方法区分释放速率差异的能力。因此，在可行的情况下，理想的情况是，IVRT方法选择性的补充论证是确认与配方相关的释放速率差异，而不是产品规格。

Determination of inequivalence between release rates should be evaluated using the statistical approach described in USP General Chapter<1724>. Specifically, the release rates from 6 cells dosed with the nominal reference strength formulation should be compared with the release rates from 6 cells dosed with an altered formulation, also at the nominal reference strength, using the statistical approach described in USP General Chapter<1724>. All 12 cells being compared should have been run in parallel on the same day, and the release rate from the altered formulation at the same nominal reference strength should fail to show equivalence to the release rate from the nominal reference strength formulation.

采用USP<1724>中描述的统计学方法对释放速率之间的不等效性进行评估。具体来说，将对照标示规格配方制剂与具有相同规格、不同配方制剂的各6杯释放速率，按USP<1724>中描述的统计学方法进行比较。所有12杯应在同一天平行运行，具有相同规格、不同配方制剂的释放速率应与对照标示规格配方制剂的释放速率不等效。

The altered formulation used in the assessment of supplemental selectivity should have the same nominal strength as the reference topical product, and may include changes in inactive ingredients, changes in inactive ingredient concentration(s), changes in the manufacturing processes, or combinations thereof. However, not all variations in a formulation will necessarily produce a difference in the release rate compared to the reference formulation, and if two similar formulations are found to have equivalent release rates, the demonstration of supplemental selectivity may be inconclusive. Therefore, applicants are encouraged to develop or select an altered formulation for the demonstration of supplemental selectivity based on differences in physicochemical and structural properties of the formulation (relative to the reference formulation) that are likely to alter the release rate of the active ingredient from the formulation. The altered formulation may be a marketed topical product, such as a different dosage form at the same strength of the same drug (e.g., a 5% gel versus a 5% ointment). Product batch information for all topical product lots used in IVRT method development, and validation studies, as applicable, should be submitted in the study reports. The topical product information should include, but not be limited to, information about the batch formula, manufacturing date, batch size, altered manufacturing processes (if applicable) and, if available, potency and content uniformity.

在补充选择性评估中，与对照外用制剂具有相关规格、不同配方的制剂，可改变的特性可能包括：非活性成分、非活性成分的浓度、生产工艺或它们的组合。然而，与对照配方制剂相比，并不是所有的配方变更都会产生不同的释放速率；如果两个相似的配方制剂具有相同的释放速率，则不适于论证IVRT方法的补充选择性。因此，鼓励申请人根据配方（相对于对照配方）的理化和结构特性的差异，开发或选择一种可能会改变活性成分释放速率的配方，去论证IVRT方法的补充选择性。变更后的配方可以是已上市的外用制剂，例如，具有相同活性成分、相同规格的不同剂型（如5%凝胶剂和5%软膏剂）。如适用，应在研究报告中递交，IVRT方法开发和验证研究中用到的所有外用制剂的相关批信息，包括但不限于：批配方、生产日期、批量、变更的生产工艺（如适用），以及效价和含量均匀度（如有）。

## ****J. Robustness 耐用性****

The IVRT method may be considered robust to a variation in the test method if the average slope of an IVRT run under the altered IVRT method parameters is within ± 15% of the average slope of the precision and reproducibility IVRT runs. Robustness testing may encompass variations in the IVRT method that are relevant to the equipment and test method, for example:

在改变IVRT方法参数后，如果IVRT的平均斜率在“精密度和重现性”研究中获得平均斜率的±15%范围内，则认为IVRT方法对于该参数的改变具有耐用性。耐用性测试可能包括与IVRT方法相关的设备和测试方法的改变，如：

* Temperature variations (e.g., - 1°C and +1°C relative to 32°C ± 1°C)
* 温度变化（如，相对32℃±1℃的-1℃和+1℃）
* Dose volume variations (e.g., +10% and -10% in the dose volume)
* 上样体积变化（如，上样体积的±10%）
* Receptor solution variations (e.g., slight change in composition and/or pH)
* 接收介质变化（如，轻微改变组成和/或pH）
* Mixing rate variation (e.g., slight change in stirring speed, as applicable)
* 混合速率变化（如，轻微改变搅拌速率，如适用）

**Sample Analytical Method Validation**

**样品分析方法验证**

While exploratory studies performed during IVRT method development may use an unvalidated sample analytical method, it is essential that all studies conducted as part of the IVRT method validation use a validated sample analytical method. A validated IVRT method should use a validated receptor solution sample analytical method. Therefore, a discussion of the sample analytical method for the IVRT method is included in this guidance under this section.

虽然在IVRT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IVRT方法验证的一部分，在IVRT方法验证时，必须采用已验证的样品分析方法。已验证的IVRT方法应当使用已验证的接收液样品分析方法。因此，该部分讨论用于IVRT方法的样品分析方法。

It is important to note that the study protocols and reports related to the IVRT method are distinct from those for the sample analytical method that is used to quantify drug concentrations in IVRT receptor solution samples. The validation of a sample analytical method, in and of itself, does not demonstrate the validity of an IVRT method. Separate and specific reports should be submitted for the validation of the sample analysis (e.g., HPLC or UPLC) method and for the validation of the IVRT method.

需要注意的是，与IVRT方法相关的研究方案和报告与用于IVRT接收液中样品定量的分析方法不同。样品分析方法验证，就其本身而言，并不能证明IVRT方法的有效性。因此，应分别递交样品分析方法（如，HPLC或UPLC）和IVPT方法的验证报告。

Any results from studies of the IVRT method that are performed (during method development) using a different sample analytical method than that which is ultimately validated, cannot support a demonstration of the validity of the IVRT method. Information should be provided in the IVRT method validation report referencing the (separate) sample analytical method validation, and clearly indicate that all relevant results in the IVRT method validation report were obtained using a validated sample analytical method (as opposed to an 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IVRT方法研究结果不能用于支持论证IVRT方法的有效性。在IVRT方法验证报告中，应提供参考的样品分析方法验证信息，并明确表明IVRT方法验证报告中的所有相关结果均是采用经验证的样品分析方法（而不是与经验证的分析方法具有不同参数的样品分析方法）获得的。

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

接收液中样品的分析方法，通常为HPLC或UPLC，应使用具有审计追踪的色谱软件（如，色谱数据系统），并应包括具有适当质量控制样品的多点（6～8个）校准曲线，同时，应符合FDA生物分析方法验证行业指南要求。

The validation of the receptor sample analytical method should include relevant qualifications of dilution integrity, if applicable, as well as stability assessments with the highest relevant temperature in the receptor solution for the longest relevant duration; the highest relevant temperature may be warmer than the IVRT membrane surface temperature because the temperature of the receptor solution is often higher than the temperature at the surface of the membrane (e.g., the temperature of the receptor solution may be 34°C when the temperature of membrane surface is 32°C, so stability assessments with the IVRT receptor solution may be performed at 34°C for 6 hours; the temperature would be higher for an IVRT with a vaginal gel, for example).

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长相关时间的稳定性评估；最高相关温度可以略高于IVRT膜表面温度，因为接收液的温度通常高于膜表面温度（例如，当膜表面温度为32℃时，接收液温度可能是34℃，因此，IVRT接收液的稳定性评估可以设定为34℃维持6小时；而在阴道凝胶制剂的IVRT研究中，温度会更高）。

# ****IVRT Pivotal Study IVRT****

# ****正式研究****

The IVRT pivotal study comparing the drug release rates between the test and reference topical products should be performed in a manner compatible with the general procedures and statistical analysis method specified in USP General Chapter<1724>. The cumulative amount of drug released at each sampling time point should be reported for each diffusion cell. Relevant summary statistics for the IVRT study should also be reported.

在IVRT正式研究中，应根据USP <1724>规定的一般程序和统计分析方法，对自研制剂和对照外用制剂的药物释放速率进行比较。应报告每个扩散池在各时间点的累计释放量。还应报告IVRT研究的相关汇总统计数据。

## ****Handling and Retention of Samples****

## ****样品的处理和保存****

Refer to 21 CFR 320.38, 320.63 and the guidances for industry Handling and Retention of BA and BE Testing Samples (May 2004) and Compliance Policy for the Quantity of Bioavailability and Bioequivalence Samples Retained Under 21 CFR 320.38(c) (August 2020), as applicable, regarding considerations for retention of study drug samples and to 21 CFR 320.36 for requirements for maintenance of records of BE testing. Retention samples should be randomly selected from the drug supplies received before dispensing during the IVRT study in which the test topical product and RS are compared. Experimental observations that may have the potential to influence the interpretation of the study results, as well as any protocol deviations, should be reported.

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月）和《21 CFR 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IVRT对比研究前，应从收到的药品中随机选择样品进行留样。应报告可能影响研究结果解释的试验观察，以及任何与方案发生的偏离。

## ****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 appropriately controlled. Also, experimental observations that may have the potential to influence the interpretation of the study results, as well as any protocol or standard operating procedure (SOP) deviations, should be 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，以及任何与方案或标准操作规程（SOP）发生的偏离。

In addition, investigators should perform the IVRT validation and pivotal studies within a quality management 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IVRT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 procedures and recording of experimental observations or deviations from procedures specified in the study protocol or 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, including study sample handling and storage records (e.g., sample tracking logs), audit trails for sample analysis 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）、样品分析过程的审计跟踪、研究物料和试剂的控制以及电子数据控制

Archival of study records

研究记录归档

**Blinding Procedure**

**盲法程序**

A detailed description of the blinding procedure should be provided in the study protocol and final report for the IVRT pivotal study. The packaging of the test topical product and RS should be similar in appearance to maintain adequate blinding of the investigator and any experimental operators. Once blinded, the test topical product and RS should be identified by a random designation, e.g., “A” or “B.”

应在IVRT正式研究的研究方案和最终报告中，提供盲法程序的详细描述。自研外用制剂和RS的包装应有相似的外观，以确保对研究人员和任何试验操作人员充分致盲。对于盲法程序，自研外用制剂和RS应随机命名，如：“A”或“B”。

## ****Dosing****

## ****上样****

In the IVRT pivotal study, the test topical product and RS should be dosed in an alternating pattern on successive diffusion cells. There are two possible sequences for the alternating pattern (either ABABAB or BABABA). One of these two dosing sequences should be randomly selected.

在IVRT正式研究中，可以在扩散池上以交替给药方式依次放置自研外用制剂和RS。有两种可供选择的交替模式（ABABAB 或 BABABA）。可随机选择上述两种方式中的一种。

# ****Submitting Information on IVRT Studies in an ANDA****

# ****ANDA中递交的IVRT研究信息****

For IVRT studies with topical products submitted in ANDAs that are intended to support a demonstration of BE, detailed study protocols, relevant SOPs, and detailed reports should be submitted for the IVRT method validation and the IVRT pivotal study. In addition, a detailed report describing the IVRT method development should be submitted. These protocols, SOPs, and reports should be 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IVRT研究，在ANDA申请中应递交IVRT方法验证和IVRT正式研究的详细研究方案、相关SOPs和报告。此外，应递交描述IVRT方法开发的详细报告。这些方案、SOPs和报告应在电子通用技术文件（eCTD）的模块5.3.1.2中递交，并对相关的试验方法、研究控制、质量管理程序和数据分析进行描述。

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

注意：用于IVRT接收液中样品浓度的定量分析方法（如，HPLC或UPLC方法）与IVRT方法相关的研究方案、SOPs和报告不同。应单独递交样品分析方法验证的方案和SOPs。样品分析方法开发和验证报告、正式IVRT研究样品分析报告，以及与IVRT研究相关的样品分析SOPs和方案，应在eCTD的模块5.3.1.4中递交。