（中英对照）美国 FDA
分析方法验证指南

目 录

I. INTRODUCTION

This guidance provides recommendations to applicants on submitting analytical procedures, validation data, and samples to support the documentation of the identity, strength, quality, purity, and potency of drug substances and drug products.

1. 绪论

本指南旨在为申请者提供建议，以帮助其提交分析方法，方法验证资料和样品用于支持原料药和制剂的认定，剂量，质量，纯度和效力方面的文件。

This guidance is intended to assist applicants in assembling information, submitting samples, and presenting data to support analytical methodologies. The recommendations apply to drug substances and drug products covered in new drug applications (NDAs), abbreviated new drug applications (ANDAs), biologics license applications (BLAs), product license applications (PLAs), and supplements to these applications.

本指南旨在帮助申请者收集资料，递交样品并资料以支持分析方法。这些建议适用于 NDA，ANDA，BLA，PLA 及其它们的补充中所涉及的原料药和制剂。

The principles also apply to drug substances and drug products covered in Type II drug master files (DMFs). If a different approach is chosen, the applicant is encouraged to discuss the matter in advance with the center with product jurisdiction to prevent the expenditure of resources on preparing a submission that may later be determined to be unacceptable.

这些原则同样适用于二类 DMF 所涉及的原料药和制剂。如果使用了其它方法，鼓励申请者事先和 FDA 药品评审中心的官员进行讨论，以免出现这种情况，那就是花了人力物力所准备起来的递交资料后来发现是不可用的。

The principles of methods validation described in this guidance apply to all types of analytical procedures. However, the specific recommendations in this guidance may not be applicable to certain unique analytical procedures for products such as biological, biotechnological, botanical, or radiopharmaceutical drugs.

本指南中所述的分析方法验证的原则适用于各种类型的分析方法。但是，本指南中特定的建议可能不适用于有些产品所用的特殊分析方法，如生物药，生物技术药，植物药或放射性药物等。

For example, many bioassays are based on animal challenge models, 39

immunogenicity assessments, or other immunoassays that have unique features that should be considered when submitting analytical procedure and methods validation information.

比如说，许多生物分析是建立在动物挑战模式，免疫原性评估或其它有着独特特性的免疫分析基础上的，在递交分析方法和分析方法验证资料时需考虑这些独特的性质。

Furthermore, specific recommendations for biological and immunochemical tests that may be necessary for characterization and quality control of many drug substances and drug products are beyond the scope of this guidance document.

而且，许多原料药和制剂的界定和质量控制所需的生物和免疫化学检测并不在本指南的范围之内。

Although this guidance does not specifically address the submission of analytical procedures and validation data for raw materials, intermediates, excipients, container closure components, and other materials used in the production of drug substances and drug products, validated analytical procedures should be used to analyze these materials.

尽管本指南并不专门叙述原料，中间体，赋形剂，包装材料及原料药和制剂生产中所用的其它物料的分析方法及分析方法验证资料的递交，但是应该应用验证过的分析方法来分析检测这些物质。

For questions on appropriate validation approaches for analytical procedures or submission of information not addressed in this guidance, applicants should consult with the appropriate chemistry review staff at FDA.

对于本指南中未提及的关于分析方法验证和资料提交方面的问题，请向 FDA 相关的化学评审人员咨询。

This guidance, when finalized, will replace the FDA guidance for industry on Submitting Samples and Analytical Data for Methods Validation (February 1987).

本指南，一旦定稿，将取代 FDA 于 1987 年 2 月份发布的工业指南：分析方法验证所需提交的样品和分析资料。

II. BACKGROUND

Each NDA and ANDA must include the analytical procedures necessary to ensure the identity, strength, quality, purity, and potency of the drug substance and drug product, including bioavailability of the drug product (21 CFR 314.50(d)(1) and 314.94(a)(9)(i)).

II. 背景

每个 NDA 和 ANDA 都必需包括必要的分析方法以确保原料药和制剂的认定，剂量，质量，纯度和效力，还包括制剂的生物利用度(21 CFR 314.50(d)(1) 和 314.94(a)(9)(i))。

Data must be available to establish that the analytical procedures used in testing meet proper standards of accuracy and reliability (21 CFR 211.165(e) and 211.194(a)(2)).

必须要有资料来论证所用的分析方法是符合一定的准确度和可靠性标准的。

Methods validation is the process of demonstrating that analytical procedures are suitable for their intended use. The methods validation process for analytical procedures begins with the planned and systematic collection by the applicant of the validation data to support the analytical procedures.

分析方法验证是论证某一分析方法适用于其用途的过程。分析方法的验证过程是从申请者有计划地系统性收集验证资料以支持分析方法开始的。

The review chemist evaluates the analytical procedures and validation data submitted in the NDA or ANDA.

审评化学家会对 NDA 或 ANDA 中的分析方法和验证资料进行评审。

On request from FDA, an NDA or ANDA applicant must submit samples of drug product, drug substance, noncompendial reference standards, and blanks so that the applicant's drug substance and drug product analytical procedures can be evaluated by FDA laboratories (21 CFR 314.50(e) and 314.94(a)(10)).

一旦 FDA 有要求，则 NDA 或 ANDA 的申请者必须提交制剂，原料药，非药典对照品和空白以使 FDA 实验室能对申请者所用分析方法进行评审(21 CFR 314.50(e) and 314.94(a)(10))。

The FDA laboratory analysis demonstrates that the analytical procedures are reproducible by laboratory testing. The review chemists and laboratory analysts determine the suitability of the analytical procedures for regulatory purposes.

FDA 实验室的分析会论证该分析方法在实验室内是可以重现的。审评化学家和实验室分析家会从法规的角度确定该分析方法的适用性。

FDA investigators inspect the analytical laboratory testing sites to ensure that the analytical procedures used for release and stability testing comply with current good manufacturing practices (CGMPs) (21 CFR part 211) or good laboratory practices (GLPs) (21 CFR part 58), as appropriate.

FDA 检查官会对分析实验室进行检查确保用于放行和稳定性实验的分析方法符合现行的 GMP（21CFR part 211) 和 GLP (21 CFR part 58)。

Each BLA and PLA must include a full description of the manufacturing methods, including analytical procedures, that demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency (21 CFR 601.2(a) and 601.2(c)(1)(iv)).

每个 BLA 和 PLA 都必须要有详细的生产工艺描述，包括分析方法，以说明所生产的产品是符合规定睥安全，纯充和效力标准的(21 CFR 601.2(a) and 601.2(c)(1)(iv))。

Data must be available to establish that the analytical procedures used in testing meet proper standards of accuracy and reliability (21 CFR 81

211.194(a)(2)). For BLAs, PLAs, and their supplements, the analytical procedures and their validation are submitted as part of the license application or supplement and are evaluated by the review committee.

必须要有资料证明所用的分析方法是符合一定的准确度和可靠性要求的(21 CFR 81

211.194(a)(2))。对于 BLA，PLA 及它们的补充，在所提交的许可证申请中应当要有分析方法和方法验证这部分的资料，审评委员会会对这部分资料进行评审。

Representative samples of the product must be submitted and summaries of results of tests performed on the lots represented by the submitted sample must be provided (21 CFR 601.2(a) and 601.2(c)(1)(vi)). The review committee chair may request analytical testing by CBER laboratory analysts to evaluate the applicant=s analytical procedures and verify the test results.

需提供代表性样品及该样品所代表批号的检测结果总结(21 CFR 601.2(a) and 601.2(c)(1)(vi))。评审委员会主席会要求 CBER 实验室的分析人员进行分析实验对申请者的分析方法进行评估，并确认其分析结果。

All analytical procedures are of equal importance from a validation perspective. In general, validated analytical procedures should be used, irrespective of whether they are for in-process, release, acceptance, or stability testing. Each quantitative analytical procedure should be designed to minimize assay variation.

从验证的角度来看，所有的分析方法有着同样的重要性。一般来说，应当要应用已验证过的分析方法，而不论其是被用于过程控制，放行，合格或稳定性实验。高等每个定量分析方法时都应当要减少其分析误差。

Analytical procedures and validation data are submitted in the sections of the application on analytical procedures and controls. Recommendations on information to be submitted are included in sections III through IX and XI of this guidance. Information on submission of the methods validation package to the NDA or ANDA and samples to the FDA laboratories is provided in section X.

分析方法和验证资料应当摆在申请的分析方法和控制章节中提交。本指南的第 III 到 IX 章和 XI 章给出了所需提供资料方面的建议。向 FDA 实验室提供样品和递交 NDA 和 ANDA 中的分析方法验证资料的信息见第 X 章。

III. TYPES OF ANALYTICAL PROCEDURES

A. Regulatory Analytical Procedure A regulatory analytical procedure is the analytical procedure used to evaluate a defined characteristic of the drug substance or drug product. The analytical procedures in the U.S. Pharmacopeia/National Formulary (USP/NF) are those legally recognized under section 501(b) of the Food, Drug, and Cosmetic Act (the Act) as the regulatory analytical procedures for compendial items. For purposes of determining compliance with the Act, the regulatory analytical procedure is used.

III. 分析方法的类型

A. 法定分析方法

法定分析方法是被用来评估原料药或制剂的特定性质的。USP/NF 中的分析方法是法定的用于药典项目检测的分析方法。为了确认符合法规，需使用法定分析方法。

B. Alternative Analytical Procedure

An alternative analytical procedure is an analytical procedure proposed by the applicant for use instead of the regulatory analytical procedure. A validated alternative analytical procedure should be submitted only if it is shown to perform equal to or better than the regulatory analytical procedure.

B. 替代分析方法

替代分析方法是申请者提出用于代替法定分析方法的分析方法。只有当一替代分析方法相当于或优于法定分析方法时，才可以应用验证过的替代分析方法。

If an alternative analytical procedure is submitted, the applicant should provide a rationale for its inclusion and identify

its use (e.g., release, stability testing), validation data, and comparative data to the regulatory analytical procedure.

如果提交了替代分析方法，申请者还应当提供其理由，并标明其用途（如，放行，稳定性实验），验证资料及其与法定分析方法的对比资料。

C. Stability-Indicating Assay

A stability-indicating assay is a validated quantitative analytical procedure that can detect the changes with time in the pertinent properties of the drug substance and drug product.

C. 稳定性指示分析

稳定性指示分析是能检测出原料药或制剂的某些性质随着时间的延长而出现的变化的定量分析方法。

A stability-indicating assay accurately measures the active ingredients, without interference from degradation products, process impurities, excipients, or other potential impurities。

稳定性指示分析能不受降解产物，工艺杂质，赋形剂或其它潜在杂质的影响而准确测定其中的活性成分。

If an applicant submits a non-stability-indicating analytical procedure for release testing, then an analytical procedure capable of qualitatively and quantitatively monitoring the impurities, including degradation products, should complement it. Assay analytical procedures for stability studies should be stability-indicating, unless scientifically justified.

如果申请者递交了用于放行检测的非稳定性指示分析方法，则应当要有能定性和定量地监测杂质，包括降解产物，的分析方法对其进行补充。稳定性试验中所用的含量分析方法应当要有稳定性指示能力，除非有科学的理由能证明其合理性。

IV. REFERENCE STANDARDS

A. Types of Standards

A reference standard (i.e., primary standard) may be obtained from the USP/NF or other official sources (e.g., CBER, 21 CFR 610.20). If there are questions on whether a source of a standard would be considered by FDA to be an official source, applicants should contact the appropriate chemistry review staff. When there is no official source, a reference standard should be of the highest possible purity and be fully characterized.

IV 标准品

A. 标准品的类型

可以从 USP/NF 处或其它官方(比如说，CBER，21CFR 610.20)获得标准品 (也就是一级对照品)。如果不能确定一标准品的来源是否会被 FDA 认为是官方来源，申请者应当要向适当的化学评审人员咨询。如果没有官方来源，则被用来作标准品的物质应当要有尽可能高的纯度，并得到充分界定。

A working standard (i.e., in-house or secondary standard) is a standard that is qualified against and used instead of the reference standard.

工作对照品 (也就是内部标准品或二级标准品)是根据一级对照品标定的，并用来代替一级对照品的。

B. Certificate of Analysis

A certificate of analysis (COA) for reference standards from non-official sources should be submitted in the section of the application on analytical procedures and controls. For standards from official sources, the user should ensure the suitability of the reference standard. The standard should be stored correctly and used within the established use interval.

B．分析报告单

对于非官方标准品，在申请的分析方法和控制章节中应当要提供该标准品的分析报告单。对于从官方获得的标准品，用户应当要确保标准品的适用性。应当正确储存标准品并在已确定的时间段内使用该标准品。

C. Characterization of a Reference Standard

Reference standards from USP/NF and other official sources do not require further characterization. A reference standard that is not obtained from an official source should be of the highest purity that can be obtained by reasonable effort, and it should be thoroughly characterized to ensure its identity, strength, quality, purity, and potency.

C．标准品的界定

从 USP/NF 及其它官方来源获得的标准品是不需要进一步界定的。非官方对照品要有尽可能高的纯度，并进行充分地界定以确保其结构，剂量，质量，纯度和效力。

The qualitative and quantitative analytical procedures used to characterize a reference standard are expected to be different from, and more extensive than, those used to control the identity, strength, quality, purity, and potency of the drug substance or the drug product. Analytical procedures used to Draft — Not for Implementation characterize a reference standard should not rely solely on comparison testing to a previously designated reference standard.

用于界定标准品的定性和定量分析方法应当要不同于用于控制原料药或制剂的结构，剂量，质量，纯度和效力的分析方法，要比它们更深入。用于标准品界定的分析方法不应仅仅是和先前的指定标准品进行比较实验。

Generally, this characterization information should include:

A brief description of the manufacture of the reference standard, if the manufacturing process differs from that of the drug substance. Any additional purification procedures used in the preparation of the reference standard should be described.

一般来说，界定资料应当要包括：

标准品的简单工艺描述，如果其生产工艺是否于其相应的原料药的话。应当要叙述制备标准品时所用的补充精制过程。

Legible reproductions of the relevant spectra, chromatograms, thin-layer chromatogram (TLC) photographs or reproductions, and other appropriate instrumental recordings. Data establishing purity. The data should be obtained by

using appropriate tests, such as TLC, gas chromatography (GC), high-pressure liquid chromatography (HPLC), phase solubility analysis, appropriate thermometric analytical procedures, and others as necessary.

相关光谱图，色谱图，TLC 照片及其它仪器输出的清晰复印件。

建立纯度的资料。应当要应用适当的检测方法来获得这些资料，比如说 TLC，GC，HPLC，相溶解分析，适当的热分析方法及其它必要的分析方法。

Appropriate chemical attribute information, such as structural formula, empirical formula, and molecular weight. Information to substantiate the proof of structure should include appropriate analytical tests, such as elemental analysis, infrared spectrophotometry (IR), ultraviolet spectrophotometry (UV), nuclear magnetic resonance spectroscopy (NMR), and mass spectrometry (MS), as well as applicable functional group analysis. Detailed interpretation of the test data in support of the claimed structure should be provided.

适当的化学性质资料，比如结构式，经验式和分子量等。结构确证资料应当要包括适当的分析测试，比如元素分析，IR，UV,NMR 和 MS，及适用的官能团分析。还应当要提供具体的结构解析资料。

A physical description of the material, including its color and physical form. Appropriate physical constants such as melting range, boiling range, refractive index, dissociation constants (pK values), and optical rotation. A detailed description of the analytical procedures used to characterize the reference standard.

物理性质的描述，包括颜色和物理形态。

适当的物理常数，比如说熔程，沸程，折射率，离解常数(pK 值)和旋光度。

用于界定标准品的分析程序的详细叙述。

For biotechnological/biological product reference standards, the recommendations on characterization information above may apply and should be considered. However, additional and/or different tests would be important to assess physicochemical characteristics, structural characteristics, biological activity, and/or immunochemical activity.

至于生物技术/生物产品的标准品，应当要考虑上述建议，可能可以应用。然而，其它确定物理化学性质，结构特性，生物活性和/或免疫化学活性的补充检测和/或其它检测将是非常重要的。

Physicochemical determinations may include isoform, electrophoretic, and liquid chromatographic patterns, as well as spectroscopic profiles. Structural characterization may include a determination of amino acid sequence, amino acid composition, peptide map, and carbohydrate structure. Biological and/or immunochemical activity should be assessed using the same analytical procedures used to determine product potency.

物理化学性质包括异构体，电泳和液相色谱行为及光谱性质等。结构界定可能包括氨基酸序列，氨基酸组成，缩氨酸图和碳水结构。确定生物和/或免疫化学活性的分析方法应当要和用来确定产品效力的分析方法一样。

These can include animal-based, cell culture-based, biochemical, or ligand/receptor-binding assays. While these tests may be needed for complete characterization of certain reference standards, specific recommendations for validation of

biological and immunochemical tests are not contained in this guidance document.

这些分析方法可以包括基于动物的，细胞培养的，生物化学的或配位体/接受体螯合的分析方法。如果这些检测需用于某些标准品的界定，生物和免疫化学检测的分析方法验证方面的特殊建议并不在本指南的范围之内。

V. METHODS VALIDATION FOR INDs

For an investigational new drug, sufficient information is required in each phase of an investigation to ensure proper identification, quality, purity, strength, and/or potency. The amount of information on analytical procedures and methods validation necessary will *var*y with the phase of the investigation (21 CFR 312.23(a)(7)).

V．IND中的分析方法验证

对于 IND 而言，每个阶段的研究都需要有足够的资料以确保合适的认定，质量，纯度，剂量和/或效力。所需的分析方法和方法验证方面的资料会随着研究的阶段变化而变化(21 CFR 312.23(a)(7))。

For general guidance on analytical procedures and methods validation information to be submitted for phase 1 studies, sponsors should refer to the FDA guidance for industry on Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well- Characterized, Therapeutic, Biotechnology-Derived Products (November 1995).

关于在第 1 阶段研究所需提交的分析方法和方法验证资料方面的指南，发起人可以参考 FDA 的指南：药品（包括结构确定的，有疗效的，生物技术产品）第 1 阶段研究的 IND 申请的内容和格式（1995 年 11 月）。

General guidance regarding analytical procedures and methods validation information to be submitted for phase 2 or phase 3 studies will be provided in the FDA guidance for industry INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products, Chemistry, Manufacturing, and Controls Content and Format, when finalized (draft guidance published April 1999).

关于在关于在第 2 和第 3 阶段研究所需提交的分析方法和方法验证资料方面的指南，发起人将可以参考 FDA 的指南：药品（包括结构确定的，有疗效的，生物技术产品）第 1 阶段研究的 IND 申请的 CMC 内容和格式（草案，1999 年 4 月）。

All analytical procedures should be fully developed and validation completed when the NDA, ANDA, BLA, or PLA is submitted.

在递交 NDA，ANDA，BLA 或 PLA 时，所有的分析方法都应当要开发出来，并得到验证。

VI. CONTENT AND FORMAT OF ANALYTICAL PROCEDURES FOR NDAs, 230

ANDAs, BLAs, AND PLAs

Any analytical procedure submitted in an NDA, ANDA, BLA, or PLA should be described in sufficient detail to allow a competent analyst to reproduce the necessary conditions and obtain results comparable to the applicant=s. Aspects of the analytical procedure that require special attention should be described.

VI．NDA，ANDA，BLA和PLA中分析方法的内容和格式

NDA，ANDA，BLA 和 PLA 中所提交的任一分析方法都应当要有详细的描述，以使合格的分析人员能重现出所需的实验条件并获得和申请者相当的实验结果。应当要叙述分析方法中需要特殊注意的地方。

If the analytical procedure used is in the current revision of the USP/NF or other FDA recognized standard references (e.g., AOAC International Book Of Methods) and the referenced analytical procedure is not modified, a statement indicating the analytical procedure and reference may be provided rather than a description of the method (21 CFR 211.194).

如果所用的分析方法是 USP/NF 或其它 FDA 认可参考文献（如，<<AOAC 国际方法汇编>>）中且所参考的分析方法未经过修改的话，则需提供该分析方法的参引，而不用提供该分析方法的描述（21 CFR 211.194）。

A description of analytical procedures from any other published sources should be provided, because the referenced sources may not be readily accessible to the reviewer.

对于从其它公开发表的文献上获得的分析方法，应当要对其进行叙述，因为评审官可能并不能很方便的获得这些文献。

分析方法描述中需要包括的典型内容如下所示：

A. Principle

A statement of the principle of the analytical procedure should be included. For example, separation is based on isocratic reversed phase HPLC with detection by UV.

B. Sampling The number of samples (e.g., vials, tablets) selected, how they are used (i.e., as individual or composite samples), and the number of replicate analyses per sample should be described.

A．基本方法

应当要说明分析方法的基本方法。比如说是用等位反相 HPLC 进行分离的，检测器为 UV 检测器。

B．取样

需要叙述的有：所选样品的数目（比如，瓶，片等），它们是如何使用的（也就是，单独的或是混合样品），每个样品分析的重复次数。

C.Equipment and Equipment Parameters

A listing of all equipment (e.g., instrument type, detector, column type, dimensions) should be included, as well as a list of equipment parameters (e.g., flow rate, temperatures, run time, wavelength settings). A drawing representing the experimental configuration (e.g., illustrating positions for a spray pattern analytical procedure) should be provided, when appropriate.

C．仪器和仪器参数

需要叙述的有：仪器列表（比如，仪器类型，检测器，柱子类型，尺寸等）和仪器参数（比如，流速，温度，

运行时间和设定波长等）。如果必要的话，还要提供实验结构示意图（比如，阐述喷洒式分析方法的位置）。

D. Reagents

A list of reagents and their grades (e.g., USP/NF, American Chemical Society (ACS) Analytical Reagent) should be included. If in-house or modified commercial reagents are used, directions for their preparation should be included. Unstable or potentially hazardous reagents should be identified, and storage conditions, directions for safe use, and usable shelf life for these reagents should be specified.

D．试剂

需要叙述的有：试剂列表及其相应的规格（比如：USP/NF，美国化学社（ACS）分析试剂）。如果使用的是自制试剂或更改过的商业试剂，则应当要有其制备方法。对于不稳定的或有潜在危险的试剂，应标明其储存条件，安全使用说明和使用周期。

E. System Suitability Testing

System suitability test parameters and acceptance criteria are based on the concept that the equipment, electronics, analytical operations, and samples to be analyzed constitute an integrated system. System suitability testing ensures that the system is working properly at the time of analysis. Appropriate system suitability criteria should be defined and included in the analytical procedure.

E．系统适应性实验

系统适应性实验参数和合格标准是建立基础是：仪器，电子元件，分析操作和待测样品是个不可分割的整体。系统适应性实验确保系统在样品分析的时候能很好地运行。在分析方法中应当要包括适当的系统适应性合格标准。

All chromatographic analytical procedures should include system suitability testing and criteria. Parameters typically used in system suitability evaluations are defined and discussed in the CDER reviewer guidance on Validation of Chromatographic Methods (November 1994).

所有的色谱分析方法都应当要有系统适应性实验及相应的合格标准。CDER 评审官指南<<色谱分析方法的验证>>（1994 年 11 月）对用于评估系统适应性的典型参数进行了定义和讨论。

System suitability testing is recommended as a component of any analytical procedure, not just those that involve chromatographic techniques. Regardless of the type of analytical procedure, testing should be used to confirm that the system will *function* correctly independent of the environmental conditions. For example, titration analytical procedures should always include the evaluation of a blank (commonly referred to as a blank titration).

建议系统适应性实验应成为所有分析方法的一部分，而不仅仅是色谱分析方法。无论是哪类分析方法，都要采用实验来证实该系统能不受环境条件的影响而正确地运行。比如说，滴定法一般来说需要进行空白实验。

F. Preparation of Standards

Procedures for the preparation of all standard solutions (e.g., stock, working standard solutions, internal standards) should be included.

F．标准品的制备

要有所有标准品溶液（比如，储备液，工作对照品溶液，内部对照品溶液）的配制方法。

G. Preparation of Samples

Sample preparation for individual tests should be clearly described. Specific details should be provided for unusual sample preparations (e.g., solid-phase extraction, derivatization).

G．样品准备每个试验的样品准备应描述清楚,不常用的样品准备应提供详细的说明。

H. Procedure

A step-by-step description of the procedure should be provided. The description should include, where appropriate, equilibration times, injection sampling sequence, and system suitability or start-up parameters. Unusual hazards should be identified.

H．操作过程

应当要按操作步骤对操作过程进行逐步叙述。叙述应当要适当包括如下信息：平衡时间，样品进样顺序和系统适应性或启动参数。需标明不常见的危险。

I.Calculations

Representative calculations, with a tabulation defining all symbols and numerical factors, and specific instructions for the calculation of degradation products and impurities should be included. Any mathematical transformations or formulas used in data analysis should be described in detail. These may include logarithmic transformations used to obtain a linear relationship from exponential data, or the use of multiple order regression analyses.

J．计算

应当要提供代表性计算公式，并要列表说明所有符号和数字系数，及计算降解产物和杂质的特殊使用说明。所有用于数据分析的数学转换或公式应详细描述。这些包括对数转换以获得指数数据的线性关系，或多元回归分析的使用。

K. Reporting of Results

K. 结果报告

1. General

The format used to report results (e.g., percent label claim, weight/weight, weight/volume, parts per million (ppm)) including the specific number of significant figures to be reported should be provided.

1．通则

应该规定关键计算步骤中的数字单位（例如，‘标签’标示量的百分比，W/W，W/L，ppm 等）

2. Impurities Analytical Procedures

The name and location/identifier (e.g., retention time (RT), relative retention time (RRT)) of impurities and the type of impurity (e.g., process, degradant, excipient degradant) should be included in the analytical procedures for impurities in the drug substance and drug product. The detection limit (DL) or quantitation limit (QL) should be stated, as appropriate. The DL or QL can be set using the drug substance's detection response.

2．杂质分析规程

在有关药物成分和产品的杂质检测规程中，应当包括杂质的名称和检测位/标志（例如，保留时间 RT，相对保留时间 RRT），以及杂质的种类（比如工艺降解产物，赋形剂降解产物），如有可能，还应当指明检测限 DL 或定量限 QL。也可以在药物成分检测中设置 DL 和 QL。

Reporting of organic impurities should cover (1) specified identified impurities by name, (2) specified unidentified impurities by location/identifier, (3) any unspecified impurities, and (4) total impurities. The total organic impurities for the drug product or drug substance is the sum of all impurities equal to or greater than their individual QL.

See recommendations regarding appropriate QLs in FDA impurities guidances (see references). Inorganic impurities and residual solvents should also be addressed.

有机杂质的报告中，应当包括：1、有记载的已经过确认的杂质的名称；2、有记载但未经过确认杂质的（检测）位/标志；3、所有的没有记载的杂质，以及；4、总杂质。总有机杂质是指所有达到或超过其自身定量限度的杂质的总量。在这里可以参考 FDA 杂质指南文章中有关判定定量限度的内容（看后面的参考）。无机杂质和溶剂的残留，也应该被提到。

For the drug product, drug substance process impurities may be excluded from reporting if an acceptable rationale is provided in the sections on analytical procedures and controls. Drug product impurities from the drug product manufacturing process, packaging, and labeling should be addressed.

对于产品以及药物成分的工艺杂质也可以不包括在报告中，除非分析规程和控制环节中描叙了一个可以被接受的原则，那么，在产品制造和包装过程中（包括贴签）产生的杂质就要被提到。

The above reporting information may not be strictly applicable to all products (e.g., biological, biotechnological, botanical, radiopharmaceutical drugs), but any significant process and product-related impurities should be determined and reported.

并不是所有产品（比如，生物制剂、生物工艺制剂、植物制剂、放射制剂）的报告都必须严格按照以上谈到的内容来写，但是所有关键的工序以及产品相关的杂质都要有检测和报告。

VII. METHODS VALIDATION FOR NDAs, ANDAs, BLAs, AND PLAs

A. Noncompendial Analytical Procedures

In an NDA, ANDA, BLA, or PLA, data must be submitted to establish that the analytical procedures used in testing meet proper standards of accuracy and reliability (21 CFR 211.194(a)(2)). Methods validation is the process of demonstrating that analytical procedures are suitable for their intended use. At the time of submission, the NDA, ANDA, BLA, or PLA should contain methods validation information to support the adequacy of the analytical procedures.

VII. NDA，ANDA，BLA和PLA中的分析方法验证

A．非药典分析方法

在 NDA，ANDA，BLA 或 PLA 中，应当要递交资料以说明检测中所用的分析方法是满足适当的准确度和可靠性要求(21 CFR 211.194(a)92))。*分析方法验证*是个论述分析方法是适用于其拟定用途的过程。在递交资料时，NDA，ANDA，BLA 或 PLA 中应当要包含分析方法验证资料以支持分析方法的准确度。

The International Conference on Harmonisation (ICH) guidance Q2A Text on Validation of Analytical Procedures (March 1995) and Q2B Validation of Analytical Procedures: Methodology (November 1996) provide recommendations on validation of analytical procedures. Analytical procedures outside the scope of the ICH guidances should still be validated.

ICH 指导原则 Q2A：分析方法验证（1999 年 3 月）和 Q2B：分析方法验证：方法学（1996 年 11 月）给出了分析方法验证的建议。对于超出 ICH 指导原则范围的分析方法也是需要验证的。

Validation Characteristics

Applicants should submit information on the validation characteristics of their

proposed analytical procedures (see ICH Q2A and ICH Q2B). Although not all of the validation characteristics are needed for all types of tests (see section VII.A.3), typical validation characteristics are:

1)验证项目

申请者应当要送交其所拟定分析方法的验证项目方面的信息（见 ICH Q2A 和 ICH Q2B)。尽管不是对于所有类型的分析方法都需要进行所有的验证项目（见第 VII.A.3 章），但还是有典型的验证项目，如：

Accuracy

Precision (repeatability and intermediate precision)

Specificity

Detection limit

Quantitation limit

Linearity

Range

Robustnes

- 准确度

- 精密度（重复性和中间精密度）
- 专属性
- 检测限
- 定量限
- 线性
- 范围
- 耐用性

2. Other Methods Validation Information

Methods validation information should also include:

Data to demonstrate the stability of all analytical sample preparations through the time required to complete the analysis.

2)其它分析方法验证信息

分析方法验证资料还应当要包括：

说明所有分析制备样品在完成分析所需的时间内的稳定性的资料。

Legible reproductions of representative instrument output or recordings (e.g., chromatograms) and raw data output (e.g., integrated areas), as appropriate.

Instrument output for placebo, standard, and sample should also be provided (see section VII.A.2.c).

清晰可读的仪器代表性输出和记录资料（如色谱图）和原始资料输出（积分面积）。安慰剂，对照品和样品的仪器输出也都是需要提供的（见第 VII.A.2.c 章）。

Representative calculations using submitted raw data, to show how the impurities in drug substance are calculated. Information from stress studies (see section VII.A.2.b). Impurities labeled with their names and location identifiers (e.g., RRT for chromatographic data) for the impurity analytical procedure.

- 代表性计算公式，以表明原料药中的杂质是如何计算的。
- 强降解实验资料（见第 VII.A.2.b 章）。

对于杂质分析方法，要标明杂质的名称和位置标识符（如，色谱中的相对保留时间 RRT）。

For drug substances:

A discussion of the possible formation and control of polymorphic and enantiomeric substances.

Identification and characterization of each organic impurity, as appropriate. This information may not be needed for all products (e.g., botanicals). Other impurities (e.g., inorganics, residual solvents) should be addressed and quantitated.

- 对于原料药：

1.讨论可能会形成的异构体并讨论异构体的控制。

对每个有机杂质进行适当的标识和界定。不是所有的产品（如，植物药）都需要这些资料的。对于其它杂质（如无机杂质，残留溶剂），应当要进行说明并定量分析。

Recommendations on submitting information on impurities is provided in *var*ious FDA guidances such as the ICH guidance Q3A Impurities in New Drug Substances (January 1996).

A list of known impurities, with structure if available, including process

impurities, degradants, and possible isomers.

1.递交杂质方法的资料可参考很多 FDA 的指导文件，如比 ICH 指导原则 Q3A *新原料药中的杂质(1996 年 1 月)*。

2.已知杂质列表，包括工艺杂质，降解产物和可能的异构体。如果知道结构的话，也需提供。

For drug products:

A degradation pathway for the drug substance in the dosage form, 419

where possible. Data demonstrating recovery from the sample matrix as illustrated

by the accuracy studies. Data demonstrating that neither the freshly prepared nor

the degraded placebo interferes with the quantitation of the active ingredient. ICH

Q2A and Q2B address almost all of the validation parameters. Areas that should be

provided in more detail are described below.

- 对于制剂：

1.原料药在制剂中可能的降解途径。

2.通过准确度实验论证的样品回收率资料。

3.要有资料论证无论是新制的安慰剂还是分解了的安慰剂都不会影响活性成分的定量分析。

ICH Q2A 和 ICH Q2B 几乎对所有的验证参数都进行了论述。下面论述的是那些还需要更详细地进行论述的方面。

a. Robustness

Robustness, a measure of the analytical procedure's capability to remain unaffected by small but deliberate *var*iations, is described in ICH Q2A and Q2B. Such testing should be performed during development of the analytical procedure and the data discussed and/or submitted. In cases where an effect is observed, representative instrument output (e.g., chromatograms) should be submitted.

a. 耐用性

ICH Q2A 和 ICH Q2B 对耐用性是有论述的，它衡量的是分析方法在细微的变化下不受影响的能力。该实验应当是在分析方法开发过程中进行的，对实验结果进行讨论和/或递交。如果观察到有影响，需提供代表性仪器输出（如色谱图）。

b. Stress Studies

Degradation information obtained from stress studies (e.g., products of acid and base hydrolysis, thermal degradation, photolysis, oxidation) for the drug substance and for the active ingredient in the drug product should be provided to demonstrate the specificity of the assay and analytical procedures for impurities. The stress studies should demonstrate that impurities and degradants from the active ingredient and drug product excipients do not interfere with the quantitation of the active ingredient. Stress studies are described in *var*ious FDA guidances relating to the stability of drug products (see references). The design of the stress studies and the results should be submitted to the stability section of the application. Representative instrument output (e.g., chromatograms) and/or other appropriate data (e.g., degradation information obtained from stress studies) should be submitted in the sections on analytical procedures and controls.

b. 强降解实验

应当要提供通过对原料药和制剂中的活性成分进行强降解实验（比如，酸性水解和碱性水解，热分解，光分解和氧化作用）得到的降解信息，以论述含量分析和杂质分析所用分析方法的专属性。强降解实验要论述的是活性成分和制剂中的赋形剂中的杂质和降解产物不会对活性成分的定量分析产生干扰。FDA 很多关于药品稳定性的指导原则都对强降解实验进行了论述。

在申请的稳定性一章中应当要提供的资料有：强降解实验设计和实验结果。而代表性仪器输出（如：色谱图）和/或其它资料（强降解实验中所得的降解信息）应当要提供在*分析方法和控制* 一章中。

c. Instrument Output/Raw Data

i. Organic Impurities

Representative data should be submitted to support an assessment of the organic impurities. Representative data for residual solvents are generally not needed. Instrument output and the raw numerical values (e.g., peak area) with appropriate identification and labeling (e.g., RT for chromatographic peaks, chemical shift (d) and coupling constant (J) for NMR) should be provided. The impurity profile should be assessed at the quantitation limit and the instrument output provided. Additional information should be provided to confirm that the impurity profile is adequately characterized. For example, a representative chromatogram using detection at a low wavelength, such as 205 nm, and double the proposed total run time could be submitted to support the specificity of the analytical procedure.

c. 仪器输出/原始资料

i.有机杂质

应当要提供代表性资料以支持有机杂质的评估。一般来说，是不需要残留溶剂的代表性资料的。仪器输出和原始数值（比如，峰面积）及合适的标记和标注（比如，色谱峰的保留时间，核磁共振的化学位移和耦合常数）都应当要提供。根据所提供的定量限和仪器输出对杂质情况进行评估。还应当要提供其它资料以确认杂质情况得到了充分地界定。比如说，比如说，代表性图谱选用的检测波长是 205nm，则可以将拟定的运行时间延长至

两倍以支持分析方法的专属性。

For quantitation purposes, the response factor of the drug substance may be used for impurities without a reference standard. In cases where the response factors are not close, this practice may still be acceptable, provided a correction factor is applied or the impurities are, in fact, being overestimated. Acceptance criteria and analytical procedures used to estimate identified or unidentified impurities often are based on analytical assumptions (e.g., equivalent detector response). Assumptions should be discussed and justified.

在定量分析时，原料药的响应因子可用于没有相应对照品的杂质。如果响应因子不接近的话，只要应用了较正因子或或者杂质实际上是被高估的话，这样做也是可行的。用于评估指定杂质或未指定杂质的合格标准和分析方法经常都是基于分析假设的（比如，相当的检测器响应）。应当要对这些假设进行讨论和合理性说明。

ii. Drug Substance

Data should be submitted showing the separation and detection of impurities using spiked or stress samples. Complete impurity profiles as graphic output (e.g., chromatograms) and raw data (e.g, integrated peak areas) of representative batches should be submitted in the sections on analytical procedures and controls for the drug substance. For ANDAs and related submissions, appropriate information for the batches used in the biobatch or submission batch should be provided. All responses (e.g., peaks) should be labeled. The analytical procedure used should be capable of differentiating changes, if any, between past and present batches. The quantitation limit and the type of organic impurity (e.g., degradant, process impurity) should be stated. The analytical procedure number, batch number, manufacturing date and site, and date of analysis should be provided.

原料药

应当要提供加样分析资料和强降解样品分析资料以表明杂质的分离和检测。在原料药的分析方法和控制一章中，应当要以图形输出的形式（比如：色谱图）提供代表性批号完整的杂质情况和原始数据（比如，积分峰面积）。对于 ANDA 和相关的递交，用于生物利用度研究的批次（biobatch）或者提交批次（submission batch）的相关资料应当要提供。所有的响应（比如，色谱峰）都应当要进行标注。

所用的分析方法应当要有能力区分先前批次和当前批次之间的变化，如果有这些变化的话。应当要说明定量限和有机杂质的类型（比如：降解物，工艺杂质）。还需提供分析方法编号，批号，生产日期和生产地点及分析日期。

iii. Drug Product

Information such as instrument output (e.g., chromatograms) and raw data (e.g., integrated peak areas) from representative batches under long-term and accelerated stability conditions, and stressed samples should be submitted in the sections on analytical procedures and controls of the drug product. For ANDAs and related submissions, appropriate information for the biobatch or submission batch should be provided. References to the raw data (e.g., chromatograms) should be included in the stability section of the application.

制剂

在制剂的分析方法和控制一章中，应要当提供的资料有：代表性批号在长期和加速稳定性实验条件下及强降解实验条件下的仪器输出（如，图谱）和原始资料（如峰面积）。对于 ANDA 和相关递交，应当要提供生物利用度实验批次或递交批次的适当资料。在申请的稳定性章节中应当要引用原始资料（比如：图谱）。

At a minimum, the submission should include instrument output and raw data for release testing and at the latest available time point for the same batch. All responses (e.g., peaks) should be labeled and identified. In addition, the analytical procedure number, batch number of the drug product, manufacturing date, date of analysis, source and batch number of drug substance, manufacturing site, and container/closure information should be provided. The analytical procedures used should be capable of differentiating changes, if any, between past and present batches. The quantitation limit and the type (e.g., degradant, leachables from packaging) should be reported. Multiple methodologies can be used.

至少，递交材料中应当要包括放行检测(Release testing)的仪器输出和原始资料. 需标注所有的响应信号（如色谱峰）。此外，还要提供，分析方法编号，制剂的批号，生产日期，分析日期，原料药的来源和批号，生产地点及容器/密闭系统信息。如在过往批次和现批次之间存在差异的话，所用的分析方法应当要有能力区分出来。应当要报告检测限和类型（如，降解物，包装时的漏出物）。

3.Recommended Validation Characteristics for Types of Tests

Table 1 is a summary of the validation characteristics that should be addressed

during validation of different types of analytical procedures. The same methodology can be used for several purposes. The validation information should support the intended purpose of the test. For example, if Raman spectroscopy is the methodology selected to quantitate polymorphic forms as impurities, or chiral HPLC for enantiomeric impurities, the recommended validation characteristics in Table 1 under quantitative testing for impurities would apply. However, if Raman spectroscopy or chiral HPLC are used for the purpose of identification or as specific tests, the recommended validation characteristics listed for those types of tests would apply.

3)各类检测的推荐验证项目

表 1 概述了在不同分析方法的验证过程中所需要的验证项目。同一分析方法可用于多个用途。验证资料需要能支持该分析方法的拟定用途。比如说，如果拉曼光谱用于定量分析多晶型杂质，或手性 HPLC 用于分析异构体杂质，则要应用表 1 中*杂质定量分析*　中所推荐的验证项目。然而，如果拉曼光谱或手性 HPLC 被用于鉴定或

特征实验的话，则要应用表 1 中所推荐的这些类型的验证项目。

表 1：不同类型检测的推荐验证项目

测类型/验证项目	鉴别	杂质检测		含量分析：溶出度（仅用于检测），含量/效价	特殊分析
		定量	限度		
准确度	—	+	—	+	+[4]
精密度—重复性	—	+	—	+	+[4]
精密度—中间精密度	—	+	—	+[1]	+[4]
专属性	+[2]	+	+	+[5]	+[4]
检测限	—	—[3]	+	—	—
定量限	—	+	—	—	—
性	—	+	—	+	—
范围	—	+	—	+	—
耐用性	—	+	—[3]	+	+[4]

NOTE:

Signifies that this characteristic is not normally evaluated.

+ Signifies that this characteristic is normally evaluated.

1 In cases where reproducibility has been performed, intermediate precision is not needed.

2 Lack of specificity for an analytical procedure may be compensated for by the addition of a second analytical procedure.

3 May be needed in some cases.

4 May not be needed in some cases.

5 Lack of specificity for an assay for release may be compensated for by impurities testing.

注：

—：表示通常不需要验证的项目。

+：表示通常需验证的项目。

1：假如已经论证了重现性，可不需要再论证中间精密度。

2：如果一分析方法缺少专属性的话，则需要另一分析方法进行补偿。

3：有些情况下是需要的。

4：有些情况下是不需要的。

Identification

Identification analytical procedures may include tests such as IR, differential scanning calorimetry (DSC), X-ray diffraction (XRD), UV, and HPLC retention time.

A specific identification test should be included for the active ingredient whenever

possible. In cases where a nonspecific identification analytical procedure is proposed for the active ingredient, two independent analytical procedures are generally sufficient, if justified. For other identification tests (e.g., a chiral HPLC retention time as confirmation for the presence of an enantiomer, chloride test for a counterion) a single test is acceptable. This concept of the number of identification tests is applicable to both the drug substance and drug product.

a. 鉴别

定性分析方法有：红外(IR)，差示热分析(DSC)，X-射线衍射(XRD)和 HPLC 保留时间。对于原料药，尽可能要有专属性强的鉴别实验，如果用的是专属性不强的定性分析方法，则通常来说运用两个独立的分析方法应当是足够的。对于其它的一些定性分析方法(如，手性 HPLC 的保留时间用于确认是否存在异构体，平衡离子的氯化物实验)，就一个检测也是可可行的。定性实验数目的概念既适用于原料药，也适用于制剂。

b. Impurities

The validation characteristics under quantitative testing for impurities, as described in Table 1, apply, regardless of which methodology is used to quantitate impurities. If the same analytical procedure is proposed as a limit test, validation characteristics under limit testing for impurities will apply.

b. 杂质

对于杂质定量分析，无论其是用什么方法来分析杂质的，都应当要验证表 1 中*杂质定量分析* 项下所说的相应验证项目。如果同样的方法还用做定性检测的分析方法的话，则要对表 1 中*杂质定性分析* 项下的验证项目进行验证。

c. Assay

Assay includes the content of the active ingredient, preservative (if used), and measurement of content in dissolution and content uniformity samples.

c. 含量

含量分析包括活性成分的含量，所用到的防腐剂的含量，及溶出度和含量均匀度检测样品的含量测定。

d. Specific Tests

Specific tests to control the drug substance, excipient, or drug product can include tests such as particle size analysis, droplet distribution, spray pattern, dissolution (excludes measurement), optical rotation, and methodologies such as DSC, XRD, and Raman spectroscopy. The validation characteristics may differ for the *var*ious analytical procedures. For example, accuracy, repeatability, intermediate precision and robustness should be evaluated for molecular size distribution gel permeation chromatography (GPC).

d. 特定实验

用于原料药，赋形剂或制剂控制的特定检测包括粒径分析，雾化状态，溶出度，旋光度和比如 DSC，XRD 及拉曼光谱等方法。不同的分析方法所需的验证项目是不尽相同的。比如说，对于凝胶渗透色谱(GPC)，需要考察其准确度，重复性，中间精密度和耐用性。

e. Compendial Analytical Procedures

The suitability of a compendial analytical procedure must be verified under actual conditions of use (21 CFR 211.194(a)(2)). Information to demonstrate that USP/NF analytical procedures are suitable for the drug product or drug substance should be included in the submission. Information on the specificity, intermediate precision, and stability of the sample solution should be included. Compendial assay analytical procedures may not be stability-indicating, and this should be considered when developing the specification (see section III.C). For compendial items, additional analytical procedures, such as impurities or osmolality, may be requested to support the quality of the drug product or drug substance. These additional analytical procedures should be validated (see section VII.A).

B. 药典分析方法

需根据实际使用条件确认药典分析方法的适用性(21CFR 211.194(a)(2))。在申请中应当要提供药典分析方法适用于该药品或原料药分析的论证资料。还应该要包括专属性，中间精密度，和样品溶液稳定性方面的资料。药典含量分析方法可能是没有稳定性指示能力的，因此在开发质量标准的过程中因当要考虑这个(见第 III.C.章)。对于药典项目，可能需要补充方法，比如杂质或渗透度，来控制制剂或原料药的质量。这些补充方法也是需要验证的(见第 VII.A.章)。

VIII. STATISTICAL ANALYSIS

A. General

Methods validation includes an assessment of the adequacy of the analytical procedure. Statistical analysis (e.g., linear regression analysis, relative standard deviation) of methods validation data is often used to demonstrate the validity of the method. The statistical procedures for the analysis of the validation data should be determined prior to the start of any validation study. The procedure followed, including the amount of data to collect and the criteria used in determining the acceptability of the analytical procedure, should be specified.

The raw methods validation data and statistical procedures used to analyze the raw data should be provided and discussed in the sections on analytical procedures and controls. All statistical procedures used in the analysis of the data

should be based on sound principles and be suitable for evaluating the dataset.

VIII. 统计分析

A. 基本原则

分析方法验证包括分析方法充分性的评估。经常对分析方法验证资料进行统计分析(比如：线性回归分析，相对标准偏差)以说明方法的正确性。在开始分析方法验证之前，应当就要确定用于验证资料分析的统计方法。还应当要规定所要遵循的程序，包括所需采集的数据量和确定分析方法合适性的合格标准。

应当要在分析方法和控制章节中提供和讨论分析方法验证原始资料和所用的统计方法。所有用于数据分析的统计程序都应当是科学的，并适用于评估该数据群的。

B. Comparative Studies

Comparative studies are performed to evaluate intermediate precision (e.g., different equipment, analysts, days). Comparative studies are also used to evaluate between laboratory *vari*ability (i.e., reproducibility) when an analytical procedure is

used in more than one laboratory or to compare and evaluate the precision and accuracy of two analytical procedures (e.

g., regulatory analytical procedure and an alternative analytical procedure). When comparative studies are performed, homo

geneous samples from the same batch should be used, if feasible. Comparative results should be statistically analyzed and

discussed and any bias explained.

B. 对比研究

开展对比研究以评估中间精密度(如，不同设备，不同分析员，不同天等)。当一分析方法会在多个实验室应用时，或要比较和评估两个分析方法(比如，法定分析方法和替代分析方法)的精密度和准确度时，也会进行对比研究以评估实验室间的差异(也就是，重现性)。在进行对比研究时，应当要尽可能地使用同一批号的均匀样品。需对对比研究的结果进行统计分析和讨论，并对偏差进行解释。

C. Statistics

For information on statistical techniques used in making comparisons, as well as other general information on the interpretation and treatment of analytical data, appropriate literature or texts should be consulted (see references) .

C. 统计

关于用于对比分析的统计技术资料，和用于分析数据处理和解析的其它基本资料，可参见相关的文献(见参考文献)

IX. REVALIDATION

When sponsors make changes in the analytical procedure, drug substance (e.g., route of synthesis), or drug product (e.g., composition), the changes may necessitate revalidation of the analytical procedures. Revalidation should be performed to

ensure that the analytical procedure maintains its characteristics (e.g., specificity) and to demonstrate that the analytical procedure continues to ensure the identity, strength, quality, purity, and potency of the drug substance and drug product, and the bioavailability of the drug product. The degree of revalidation depends on the nature of the change. When a different regulatory analytical procedure is substituted (e.g., HPLC for titration), the new procedure should be validated (see section VII).

IX. 再验证

当发起人对分析方法，原料药(比如，合成路线)，或制剂(比如，组分)作了更改的话，则需要对分析方法进行重验证。进行重验证是为了确保该分析方法仍然保持其特性(比如，专属性)，并论证说明该分析方法仍然能确保原料药和制剂的同一性，浓度/剂量，质量，纯度和功效，及制剂的生物利用度。重验证的程序取决于该变更的性质。当使用了另一个法定分析程序的话(比如，用 HPLC 代替了滴定法)，则新的分析方法也需要验证(见第 VII 章)。

If during each use an analytical procedure can meet the established system suitability requirements only with repeated adjustments to the operating conditions stated in the analytical procedure, the analytical procedure should be reevaluated, amended, and revalidated, as appropriate.

FDA intends to provide guidance in the future on postapproval changes in analytical procedures.

如果在每次使用时，都必须要对分析方法中所述的操作条件进行反复调整，才能使其符合系统适应性要求的话，则该分析方法需要适当进行重新评估，修正和重验证。

FDA 打算在将来要提供分析方法批准后变更方面的指南。

X. METHODS VALIDATION PACKAGE: CONTENTS AND PROCESSING

Part of the methods validation process may include FDA laboratory analysis to demonstrate that an analytical procedur e is reproducible by laboratory testing. A methods validation package (see X.A) and samples (see X.B) will be needed for

this process.

A. Methods Validation Package

The methods validation package will usually include information copied from pertinent sections of the application. To aid the review chemist, these copies should retain the original pagination of the application sections. For ANDA and NDA

products, the archival copy and extra copies of the methods validation packages should be submitted with the

application.

For ANDAs and related supplemental applications, one archival copy and two extra copies of the methods validation pac

kage should be submitted. For NDAs and related supplemental applications, one archival copy and three extra copies shoul

d be submitted. For BLAs and PLAs, a separate methods validation package need not be submitted. Information similar to

that specified here should be included in the BLA or PLA submission.

X．分析方法验证资料：内容和数据处理

作为分析方法验证过程的一部分，可能需要 FDA 实验室的分析以论证说明某一分析方法是能被重现的。在这个过程中将会需要分析方法验证资料(见 X.A)和样品(见 X.B)。

A．分析方法验证资料

分析方法验证资料通常会包括申请中的相关章节。为了便于评审化学家进行评审，这些资料应当要和其在原来申请中一样，包括内容和形式。

对于仿制药和新药申请所涉及的产品，在申请中应当还要提交一份分析方法验证资料的存档副本(archival copy)和其它副本。对于仿制药申请和其相关的补充申请，需要提交一份分析方法验证资料的存档副本(archival copy)和另外两份副本。对于新药申请及其相关补充申请，需要提交一份分析方法验证资料的存档副本(archival copy)和另外三份副本。对于 BLA 和 PLA，则不需要单独递交分析方法验证资料。类似的资料应当摆在 BLA 和 PLA 申请中。

The methods validation package should include:

1. Tabular List of All Samples to Be Submitted

The list should include the lot number, identity (with chemical name and structure

where required for clarity), package type and size, date of manufacture, and quantity of the samples.

2. Analytical Procedures

A detailed de*script*ion of each of the analytical procedures listed in the specifications should be submitted. The de*script*ion should be sufficient to allow the FDA laboratory analysts to perform the analytical procedure (see section VI).

3. Validation Data

Appropriate validation data to support the analytical procedures should be submitted. Individual values as well as summary tables should be provided. Representative instrument output and raw data and information regarding stress studies should be included (see section VII).

4. Results

The results obtained by the applicant for the submitted samples should be provided. Alternatively, COAs could be submitted. The dates of analysis should be stated.

5. Composition

The components and composition of the drug product should be provided.

6. Specifications

The specifications for the drug substance and the drug product should be included.

7. Material Safety Data Sheets

The applicant should include material safety data sheets (MSDSs) for all samples, standards, and reagents (29 CFR 1910.1200(g)). As appropriate, MSDSs should be provided for other materials used in the analytical procedures listed in the methods validation package. In the case of toxic or hazardous materials, MSDSs should be posted on the outside of the package to facilitate safe handling.

分析方法验证资料应当要包括：

1．所需递交样品的列表清单

清单中应当要包括批号，结构(化学名和结构式)，包装类型和大小，生产日期，样品量。

2．分析方法

质量标准中所列的所有分析方法的详细描述。方法描述应当要很充分，可以让 FDA 实验室分析人员根据这个描述进行操作。(见第 VI 章)

3．验证资料

应当要提供用于支持分析方法的验证资料。应当要提供每个分析数据及概述。还要提供典型的仪器输出资料和强降解研究资料。(见第 VII 章)

4．结果

应当要提供申请者对所提供样品所做分析的分析结果，或者提供其相应的分析报告单。需说明分析日期。

5．组分

需说明制剂的组分和组成。

6．质量标准

需提供原料药和制剂的质量标准。

7．安全数据表

申请者应当要提供所有样品，标准品和试剂的安全数据表(MSDS)(29CFR 1910.1200(g))。还要适当提供分析方法验证中所列各分析方法所有的其它物料的安全数据表(MSDS)。如果是毒性物料或危险性物料，则在外包装上要贴上 MSDS，以便于安全处理。

B. Selection and Shipment of Samples

On request from CDER, an NDA or ANDA applicant must submit samples of drug product, drug substance, noncomp endial reference standards, and blanks, so that the suitability of the applicant=s drug substance and drug product analytical

procedures can be evaluated by FDA laboratories (21 CFR 314.50(e) and 314.94(a)(10)). For BLAs and PLAs, representat

ive samples of the product must be submitted, and summaries of the results of tests performed on the lots represented by the submitted sample must be provided (21 CFR 601.2(a) and 601.2(c)(1)(vi)).

B. 样品的选择和运输

NDA 或 ANDA 申请者必须要根据药品评审和研究中心(CDER)的要求递交制剂，原料药，非药典对照品和空白，以使 FDA 实验室可以评估申请者所用制剂和原料药分析方法的适用性。(21CFR 314.50(e) 和 314.94(a)(10))。对于 BLA 和 PLA，需提交产品的代表性样品，并提供所提交样品批次的检测结果。(21CFR601.2(a)和 601.2(c)(1)(vi)).

For CDER products, the number of sets of samples that should be submitted for methods validation will be identified in the instructions forwarded to the applicant by the FDA laboratory. In general, the quantity of samples in each set should be double the amount needed to carry out the testing as performed by the applicant. Along with the drug substance and the drug product samples, the applicant should submit internal standards, non-USP reference standards, samples of impurities, degradation products, and unusual reagents. A set of samples will be shipped to each assigned laboratory.

对于 CDER 产品，FDA 实验室会告诉申请者所需递交样品的量。一般来说，样品量应当是实验用量的两倍。除了递交原料药和制剂样品之外，申请者还应当要递交内部对照品，非美国药典对照品，杂质样品，降解物和非常用试剂。应当要向每个指定的实验室寄送一系列样品。

For biological products, CBER should be consulted on the submission of samples and supporting materials.

Unless specified differently by the reviewer, samples from any batch, preferably samples from an aged batch, may be selected for NDAs and NDA supplemental applications. The submitted drug product samples should be from a batch made with the proposed market formulation. For ANDAs and appropriate supplements, a sample of the finished product from a batch being used to support approval of the submission should be used. If a sample is selected from a batch not described in the application, an amendment containing a copy of the batch record and certificate of analysis should be provided to the ANDA. For supplements that do not require submission and review of an exhibit batch record and associated data, any commercial batch may be submitted. For biological products, samples from several consecutively manufactured batches should be submitted.

对于生物制品，应当要向 CBER 咨询关于样品和支持资料的递交。

除非评审官另有说明，任一批次的样品，最好是较早批次，都可以用于新药申请及其补充申请。所递交的制剂

样品必须是根据拟定的上市配方生产的。对于仿制药申请及其相关的补充，应当要提交用于支持申请批准的制剂批次的样品。如果样品是来自于一申请中未提及的批次的话，则在 ANDA 中还应当要补充一份批记录和分析报告单的复印件。对于不需要递交申请和不需要审阅批记录及相关资料的补充，可递交任一商业批次的样品。对于生物制品，应当要提交连续几个生产批次的样品。

The drug product should be supplied in its original packaging. Bulk substances (e.g., drug substances, impurities, excipients) should be stored in opaque nonreactive containers. To prevent breakage during shipping, the samples should be adequately packaged in a sturdy container. Samples shipped from outside the United States should contain the appropriate customs forms to reduce delay in delivery.

If special storage precautions (e.g., freezing, use of an inert gas blanket) are required to protect sample integrity, arrangements should be made in advance with the validating laboratory for scheduled direct delivery. If a sample is toxic or potentially hazardous, the container should be prominently labeled with an appropriate warning and precautionary handling instructions.

应当要以其原包装提供制剂样品。而像原料药，杂质，赋形剂等，则应当要保存在不透明的惰性容器中。为了防止在运输过程中泄露，样品应当要装在耐用的容器中。如果是美国国外的样品，则应当要有适当的海关单据，以减少耽搁。

如果样品需要特殊的储存条件(比如，冷冻，惰性气体保护)，则要事先和验证实验室联系以安排直接递送。如果是毒性样品或危险性样品，则在容器的显著位置标明警示标志和预防措施。

C. Responsibilities of the *var*ious Parties

1. Applicant

In the sections of the application on analytical procedures and controls, the applicant should provide a name, address, telephone number, and facsimile number so that samples can be requested. If this information is not provided, the contact person and address listed in the NDA, ANDA, BLA, or PLA submission will be used.

The methods validation packages should be compiled and submitted with the NDA or ANDA submission. For BLAs and PLAs, a separate methods validation package need not be submitted. When an FDA laboratory contacts the applicant for samples, the applicant should provide FDA laboratories with the samples within 10 working days. With the exception of sample delivery arrangements, all communications concerning validation at the FDA laboratories should be made through or with the knowledge of the review chemist for CDER applications, or the BLA/PLA committee chair for CBER applications.

C. 各方职责

1. 申请人

在申请的分析方法和控制一章中，申请人应当要提供其名称，电话号码和传真号码以使 FDA 可以向

其发送提交样品的要求。如果没有提供这些信息的话，则会用 NDA，ANDA，BLA 或 PLA 申请中所写地址和联系人信息进行联系。

分析方法验证资料应当要和 NDA 或 ANDA 资料一起编写和递交。对于 BLA 和 PLA，则不需要递交单独的分析方法验证资料。

一旦 FDA 实验室要求申请人提交样品的话，申请人应当要在 10 个工作日将样品提供给 FDA 实验室。除了样品运送之外，所有关于在 FDA 实验室进行验证的交流工作都要当要让 CDER 申请的化学评审官知道，如果是 CBER 申请，则要让 BLA/PLA 委员会主席知道。

2. Review Chemist

The review chemist will review the application to determine that the analytical procedures are adequate to ensure the identity, strength, quality, purity, and potency of the drug substance and/or drug product. Any changes in the methods resulting from the review of the application may require resubmission of the methods validation package. The review chemist, in coordination with the appropriate FDA laboratories, will decide which analytical procedures are to be validated. Comments from the FDA laboratories, if any, will be forwarded by the review chemist to the applicant on completion of the studies by the laboratories.

2.化学评审官

化学评审官会对申请进行评审，以确定该分析方法是否能充分地确保原料药和/或制剂的同一性，浓度/剂量，质量，纯度和功效。对申请进行评审后，如要对分析方法作必要修改的话，则需要重新递交分析方法验证资料。化学评审官会和相关的 FDA 实验室进行讨论，确定需要对哪个分析方法进行验证。化学评审官会将 FDA 实验室对所做研究的意见转给申请人。

3. FDA Laboratory

An FDA laboratory will contact applicants with instructions on the submission of samples and the addresses to which samples should be mailed. The laboratory will test the samples according to the submitted analytical procedures to determine whether the analytical procedures are acceptable for quality control and suitable for regulatory purposes. Results and comments will be forwarded to the review chemist on completion of the studies.

4. Investigator

The investigator inspects the analytical laboratory testing sites where the release and stability testing are performed to ensure that the analytical procedures are performed in compliance with CGMP/GLP.

FDA 实验室

FDA 实验室会和申请者联系，告知样品递交程序和注意事项及邮寄地址。FDA 实验室会所递交的分析方法对样品进行检测，以确定该分析方法是否适用于质量控制，并符合法规要求。在完成研究之后，FDA 实

验室会将结果和意见转给化学评审官。

检查官

检查官会对进行放行检测和稳定性实验的分析实验室进行检查，以确保所做的分析检测能符合 CGMP/GLP。

XI. METHODOLOGY

Sections II through IX provide general information on the submission of analytical procedures and methods validation information, including validation characteristics. Additional information on certain methodologies is provided below.

XI．方法学

从第 II 章到第 IX 章提供了分析方法和分析方法验证资料方面的基本信息，包括验证项目。下文就一些具体的方法给出了说明：

A. High-Pressure Liquid Chromatography (HPLC)

The widespread use of HPLC analytical procedures and the multitude of commercial sources of columns and packings frequently have created problems in assessing comparability. Many of the following points may also apply to other chromatographic analytical procedures.

1. Column

The following characteristics are useful for defining a particular column and, if known, should be included in the analytical procedure de*scripti*on. If method development has indicated that columns from only one commercial source are suitable, this information should be included as part of the analytical procedure. If more than one column is suitable, a listing of columns found to be equivalent should be included.

A. 高效液相色谱(HPLC)

HPLC 分析方法的广泛应用及色谱柱和柱填充的众多来源都经常会给可比性评估带来很多问题。如下这些要点中，很多都适用于其它色谱分析方法。

1.色谱柱

在定义某一色谱柱时，如下这些性质是很有用的，也应当要包括在分析方法描述中。如果分析方法开发表明只有某一商业来源的色谱柱是适用的，则在分析方法中应当要包括这些资料。如果有多种色谱柱都是适用的话，则应当要包括等效色谱柱列表。

a. Column Parameters

! Material: glass, stainless steel, plastic

! Dimensions: length, inner diameter

! Frit size

! Filter type

! Precolumn and/or guard column type, if used

b. Packing Material

! Particle type: size, shape, pore diameter

! Surface modification (e.g., bonded surface type, surface coverage, percent carbon, additional silylation)

! Recommended pH range for column use

a 色谱柱参数

材质：玻璃，不锈钢，塑料

尺寸：长度，内径

Frit size

过滤类型

预柱和/或保护柱

b. 色谱柱填充物

颗粒类型：尺寸，形状，孔径

表面处理(如：键合表面类型，表面覆盖，碳比例，甲硅烷基化作用)

适用的 pH 范围

2. System Suitability Testing

Each analytical procedure submitted should include an appropriate number of system suitability tests defining the critical characteristics of that system. Criteria for all system suitability testing should be provided. The system suitability tests listed below are defined in CDER=s reviewer guidance on Validation of Chromatographic Methods (November 1994).

! Tailing factor

! Relative retention

! Resolution

! Relative standard deviation (RSD)

! Capacity factor

! Number of theoretical plates

2．系统适应性研究

对于每个所递交的分析方法，都应当包括适当的系统适应性研究，以确定该系统的关键特性。还要提供所有系统适应性实验的合格标准。CDER 的评审官指南：*色谱方法的验证(1994 年 11 月)* 中对如下这些系统适应性实验进行了定义：

- 拖尾因子

- 相对保留
- 分离度
- 相对标准偏差
- 容量因子

理论塔板数

The RSD is normally performed at the beginning of the run. However, for assays with lengthy run times or as otherwise justified by the applicant, the reported average may be taken from injections at the beginning and end of the run, or at the beginning, middle, and end of the run.

If an internal standard is used, the minimum acceptable resolution between the internal standard and one or more active ingredients should be specified. If the analytical procedure is used to control the level of impurities, the minimum resolution between the active ingredient and the closest eluting impurity, or the two peaks eluting closest to each other, should be given.

一般来说，在仪器开始运行时，进行进样精密度实验，计算其相对标准偏差。然而，对于运行时间很长的分析，或申请者另有理由说明，则可以在运行的开始和结束时，或在运行的开始，中间和结束时进样，然后报告其平均值。

如果用到了内标物，则应当要标明内标物与活性成分(单个或多个)之间的分离度的最低可接受值。如果该分析方法是用于控制杂质水平的，则应当要说明活性成分和最邻近杂质组分，或每两相邻组分的分离度最小可接受值。

3. Operating Parameters

The sequence of injection of blanks, system suitability standards, other standards, and samples should be defined. Flow rates, temperatures, and gradients should be described.

Complete details should be provided for the preparation of the mobile phase, including the order of addition of the reagents and the methods of degassing and filtration. The effect of adjustments in mobile phase composition on retention times should be included in the analytical procedure. The rationale for the use of precolumns and/or guard columns should be provided and justified. Any special requirements, such as the use of inert tubing or injection valves, should be specified.

3.操作参数

应当要确定空白溶液，系统适应性实验用标准溶液，或其它标准溶液和样品溶液的进样顺序。应当要对流速，温度和梯度洗脱进行描述。

需详细说明流动相的配制，包括试剂的添加顺序，去气和过滤的方法。分析方法中应当要说明流动相组成的调整会对保留时间所产生的影响。如使用了预柱和/或保护住的话，则要进行说明并提供给出合理性解释。如有任

何其它要求，如使用了惰性管(inert tubing)或进样阀(injection valve)，都应当要对此进行说明。

B. Gas Chromatography (GC)

At a minimum, the following parameters should be included in the description of a GC procedure. Additional parameters should be specified if required by the analytical procedure. If method development has indicated that columns from only one commercial source are suitable, this information should be included as part of the analytical procedure. If more than one column is suitable, a listing of columns found to be equivalent should be included.

B. 气相色谱(GC)

在 GC 分析方法描述中，至少要包括如下内容。如分析方法中用到了其它的一些参数，对此也应当要进行说明。如果分析方法开发表明只有某一商业来源的色谱柱是适用的，则在分析方法中应当要包括这些资料。如果有多种色谱柱都是适用的话，则应当要包括等效色谱柱列表。

1. Column

! Column dimensions: length, internal diameter, external diameter

! Stationary phase

! Column material (e.g., silica, glass, stainless steel)

! Column conditioning procedure

2. Operating Parameters

! Gases: purity, flow rate, pressure

! Temperatures: column, injector, detector (including temperature program, if used)

! Injection (e.g., split, splitless, on-column)

! Detector

! Typical retention time and total run time

1.色谱柱

色谱柱尺寸：柱长，内外径

固定相

材质(比如：硅酸，玻璃，不锈钢)

柱调节程序

2.操作参数

载气：纯度，流速，压力

温度：柱子，进样器，检测器(包括升温程序，如有用到的话)

进样(比如：分流，不分流，柱头进样(On-column injection)

检测限

典型保留时间和总运行时间。

3. System Suitability Testing

Appropriate system suitability criteria should be defined and included in all analytical procedures.

If an internal standard is used, the minimum acceptable resolution between the internal standard and one or more active ingredient should be specified. If the analytical procedure is used to control the level of impurities, the minimum resolution between the active ingredient and the closest eluting impurity, or the two peaks eluting closest to each other, should be given.

The RSD is normally performed at the beginning of the run. However, for assays with lengthy run times or as otherwise justified by the applicant, the reported average may be taken from injections at the beginning and end of the run, or beginning, middle, and end of the run.

3.系统适应性实验

在所有的分析方法中都应当要有适当的系统适应性要求。

如果用到了内标物，则应当要标明内标物与活性成分(单个或多个)之间的分离度的最低可接受值。如果该分析方法是用于控制杂质水平的，则应当要说明活性成分和最邻近杂质组分，或每两相邻组分的分离度最小可接受值。

一般来说，在仪器开始运行时，进行进样精密度实验，计算其相对标准偏差。然而，对于运行时间很长的分析，或申请者另有理由说明，则可以在运行的开始和结束时，或在运行的开始，中间和结束时进样，然后报告其平均值。

C. Spectrophotometry, Spectroscopy, Spectrometry and Related Physical Methodologies

These analytical procedures include, but are not limited to, IR spectrophotometry, near IR spectrophotometry (NIR), UV/visible spectrophotometry (UV/Vis), atomic emission and atomic absorption, NMR, Raman spectroscopy, MS, and XRD.

Spectrometric analytical procedures may not be stability-indicating. The bias of the analytical procedure should be evaluated by comparing it with a chromatographic procedure, where appropriate. When manually operated equipment is used, the de*scripti*on of the analytical procedure should include an acceptance criterion for the amount of time that may elapse between sampling and reading. Appropriate system suitability and/or calibration testing is recommended. Validation criteria should include specificity (demonstrating no interference of placebo), linearity, repeatability, intermediate precision, and robustness.

C. 分光光度法，光谱法和相关的物理方法

这些分析方法包括但不局限于红外光谱(IR)，近红外光说(NIR)，紫外可见光谱(UV/Vis)，原子发射光谱/原子吸收光谱，核磁共振(NMR)，拉曼光谱，质谱(MS)和 X-射线衍射(XRD)。

光谱分析方法可能没有稳定性指示能力。必要的话，可能通过与色谱方法的比较来评估光谱分析方法的偏差。

如果用到了手动仪器的话，则分析方法描述中应当要有取样(sampling)和读数(reading)之间时间差的可接受标准。

建议使用适当的系统适应性实验和/或校准实验。验证标准中应当要包括专属性(说明没有空白干扰)，线性，重复性，中间精密度和耐用性。

D. Capillary Electrophoresis (CE)

At a minimum, the parameters listed below should be specified for a capillary electrophoretic analytical procedure. Additional parameters may be included as required by the procedure.

If method development has indicated that capillaries from only one commercial source are suitable, this information should be included as part of the analytical procedure. If more than one capillary is suitable, a listing of capillaries found to be equivalent should be included.

1. Capillary

! Capillary dimensions: length, length to detector, internal diameter, external

diameter

! Capillary material

! Capillary internal coating (if any)

D. 毛细管电泳(CE)

对于一个毛细管电泳分析方法，至少要指明下述参数。如分析方法需要的话，还要包括其它参数。若方法开发研究表明只有某一商业来源的毛细管是适用的话，则在分析方法描述中需包括该信息。如果有多种毛细管柱都是适用的，则要列表说明所有的等效毛细管柱。

1．毛细管柱

毛细管尺寸：长度，至检测器长度，内径，外径

毛细管材质

毛细管内部涂层(如果有的话)

2. Operating Parameters

! Capillary preparation procedure: procedure to be followed before the first

use, before the first run of the day, before each run (e.g., flush with 100

millimolar sodium hydroxide, flush with running buffer)

! Running buffer: composition, including a detailed preparation procedure with

the order of addition of the components

! Injection: mode (e.g., electrokinetic, hydrodynamic), parameters (e.g.,

voltage, pressure, time)

! Detector

! Typical migration time and total run time

! Model of CE equipment used

! Voltage (if constant voltage)

! Current (if constant current)

! Polarity (e.g., polarity of electrode by detector)

2．操作参数

毛细管制备程序：第一次使用前，每天第一次运行前，每次运行前所要遵循的程序(比如，用 100 mmol 的氢氧化钠冲洗，或用电流缓冲液冲洗)

电泳缓冲液：组成，包括详细的制备程序及各组分的添加次序。

进样：模式(电动的，水力的)，参数(比如，电压，压力，时间等)

检测器

典型的迁移时间和总运行时间

所用的 CE 仪器

电压(如果是恒压的话)

电流(如果是恒流的话)

极性(比如，检测器电极的极性)

3. System Suitability Testing

Each analytical procedure should include the appropriate system suitability tests defining the critical characteristics of that system. Other parameters may be included at the discretion of the applicant.

If an internal standard is used, the minimum acceptable resolution between the internal standard and one or more active ingredient should be specified. If the analytical procedure is used to control the level of impurities, the minimum resolution between the active ingredient and the closest eluting impurity, or the two peaks eluting closest to each other, should be given.系统适应性实验

3．系统适应性试验

每个分析方法都应当要有适当的系统适应性实验以确定该系统的关键参数。是否包括其它参数，这由申请者来决定。

如用到了内标物，则至少要指明内标物和一个或多个活性组分间分离度的最小可接受值。若该分析方法是用于

控制杂质水平的话，则要说明活性组分的最接近流组分间的最小可接受分离度，或每两邻近组分间的最小可接受分离度。

E. Optical Rotation

Optical rotation is used for the measurement of stereochemical purity. Visual polarimeters rely on a monochromatic source, which traditionally was sodium D, but has expanded to virtually any wavelength.

If measurements are to be made at a wavelength other than sodium D, an explanation for selecting the wavelength should be given, along with a comparison of the specific rotation at sodium D and the wavelength to be used. Circular dichroism (CD) spectra may suffice for this purpose. In addition to the provisions of USP <781>, procedures for measurement of specific rotation should include the solvent, concentration, and, for aqueous solutions, the pH to which the solution should be adjusted. The conditions and equipment should be shown to be suitable to confirm the stereochemical identity of a racemate or an enantiomer.

The enantiomeric purity can be expressed as enantiomeric excess (e.e.), using the following formula as an example:

E. 旋光度

旋光度被用于测定立体化学纯度。可视旋光计依赖于单色光源，传统上是有钠 D，但事实上已扩展到使用任一波长的光源。

如果测定波长不是钠 D 的话，则要给出选择该波长的理由，并要对比在钠 D 和所选用波长下的旋光度。循环二色性图谱能达到这个目的。除了 USP<781>中的规定之外，旋光度测定程序还应当要包括溶剂，浓度，及水溶液所要调节到的 pH 值。所用仪器和条件都要能适用于消旋物或光学异构体的结构确认。

光学异构体纯度可以用异构体过量(e.e.) 来表示，举例如下：

e.e. = 100% * {{M} - [m]}/{[M] + [m]}

where [M] and [m] are the concentrations of the major and minor enantiomers, respectively. This yields values of zero for a racemate and 100 percent for a pure enantiomer. An intermediate concentration gives intermediate values; for example, 97:3 would give an e.e. of 94 percent.

Appropriate system suitability and/or calibration testing is recommended. Validation criteria should include specificity, and intermediate precision.

e.e. = 100% * {{M}-[m]}/{[M]+[m]}

式中：

[M]和[m]分别是较多光学异构体和较少光学异构体的量。对于消旋物来说，该值为 0，若

为纯的光学异构体，则为 100%。若为中间浓度，则将其表示为中间值；比如，97：3 的 e.e 为 94%。

推荐进行适当的系统适应性实验和/或校准实验。验证项目应当包括专属性和中间精密度。

Methodologies Relating to Particle Size Analysis Particle size analysis is an important element for quality control and

regulatory evaluation of certain drug substances and drug products. The normal concepts of validation may differ for particle size methodologies as compared to other analytical methodologies such as HPLC. However, a standard mixture may be used for calibration.

F. 粒径分析相关的分析方法

对于有些原料药和制剂的质量控制和官方评审来说，粒径分析是个很重要的因素。

和其它分析方法，比如 HPLC 相比，粒径分析方法的验证是不尽相同的。然而，在给验证进应用到标准混合物。

Particle size evaluation can include characteristics of size, morphology, surface, and population of particles. The following parameters are useful for describing particle size analysis for characterization of drug substances and drug products.

粒径分析可以包括尺寸特征，形态，表面和粒子群。如下这些参数对于描述界定原料药或制剂所用粒径分析时是很有用的。

Particle Size Methods

Types of particle size methods include, but are not limited to:

a. Nonfractionation methods that evaluate an entire population of particles

! Microscopy (optical, electron)

! Light scattering (dynamic, photon correlation, laser diffraction)

! Electrozone sensing

! Photozone sensing

b. Fractionation methods that use physical techniques to separate particles on the basis of size

! Sieving

! Cascade impactor

! Sedimentation

! Size exclusion chromatography

1. 粒径分析方法

粒径分析方法包括，但不局限于：

a. 评估整个粒子群的非分级方法

i. 显微镜检查法

ii. 光散射法(动态，光子相关，激光衍射)

iii. 电阻感应(Electrozone sensing)

iv. 光阻感应(Photozone sensing)

b. 根据粒子的尺寸进行分离的物理性分级方法。

i. 筛分

ii. 阶式碰撞采样器

iii. 沉降法

尺寸排除色层分析法

2. Calibration and Validation Characteristics

To ensure proper instrument operation, the system should be calibrated according to the manufacturer's and/or the laboratory's specification, as appropriate.

The methods validation usually involves evaluation of intermediate precision and robustness. Assurance should be provided that the data generated are reproducible and control the product's quality. See additional information in sections V and VII.

2.校准和验证

为了确保仪器的正确运行，应当根据生产厂家和/或实验规范进行校准。

分析方法验证经常会包括中间精密度和耐用性(robustness)的评估。应当要确保所得到的数据是可重现的，并能控制产品的质量。更多信息可参见第 V 和 VII 章

G. Dissolution

The equipment used for dissolution is covered by USP <711> or USP <724>. The dissolution procedure de*scripti*on and validation should include the following.

G. 溶出度

在 USP<711>或 USP<724>中说明了溶出度实验所用的设备。溶出度实验分析方法描述及其分析方法验证中应当包括如下资料：

1. Dissolution Medium

A brief discussion of the reasons for selecting the medium.

2. Procedure

A dissolution test consists of a dissolution procedure and method of analysis (automated on-line analysis or manual sampling followed by HPLC analysis). The written procedure should cover the following items:

! Apparatus

! Preparation of standard

! Preparation of sample

! Method of analysis (e.g., UV, HPLC)

! Sampling procedure (e.g., intervals, filtration, handling of samples, dilutions)

! Calculations

! Acceptance criteria

Regardless of the method of analysis, system suitability criteria should be described.Blank and standard solution spectra or chromatograms should be included.

1. 溶解媒介

简要讨论媒介选择的理由。

2. 操作程序

溶出度实验包括溶出程序和分析方法(自动在线分析或手动取样然后进行 HPLC 分析)。书面程序应当要包括如下这几点：

仪器

标准品的制备

样品的制备

分析方法(比如，UV，HPLC)

取样程序(比如，间隔，过滤，样品处理，稀释)

计算

合格标准

无论是用什么分析方法，都应当要有系统适应性实验，并要有相应的合格标准。还应当要有空白溶液和标准溶液的光谱或色谱图。

3.Validation Characteristics

Both the dissolution procedure and the method of analysis should be validated.

The time needed for the completion of the sample analysis should be stated in the procedure. Data should be submitted to support the stability of the dissolution sample during the procedure. If filters are used on-line or during sample preparation, appropriate recovery studies should be performed and documented and any bias should be addressed.

3.验证

无论是溶出程序，还是分析方法都应当要经过验证。

在操作程序中应当要说明完成样品分析所用的时间。还应当要有资料说明样品在实验过程中的稳定性。若进行了在线过滤或在样品制备过程中进行了过滤，则应当要进行适当的回收实验并整理成文件，需说明实验过程中出现的所有偏差。

H. Other Instrumentation

1. Noncommercial Instrumentation

FDA encourages the development and use of the most appropriate instrumentation. However, the use of rare or exotic

systems not only places an undue burden on the regulatory laboratory, but also may delay the validation process. When noncommercial instrumentation is used, the instrumentation should be capable of being constructed from commercially available components at a reasonable cost, if possible. For unique methodologies or instrumentation requiring contract fabrication, the applicant's cooperation with the FDA laboratories in helping facilitate duplication of the analytical procedure is important. In addition to design and equipment specifications, complete performance assessment procedures should be provided. Such systems may be found suitable for regulatory use.

H. 其它仪器分析方法

非商业化仪器

FDA 鼓励开发和使用最恰当的仪器。稀有系统的使用不仅给官方实验室带来了过度的负担，也会耽搁验证过程。若使用非商业化仪器，则应当尽可能地能以经济的商业化配件组装成实验所用仪器。对于需要合同制造的特殊分析方法或仪器，申请者应当要和 FDA 实验进行合作，以使该分析方法可以重现，这一点是非常重要的。除了需提供仪器设计和仪器规格之年，还应当要提供完整的性能评估程序。这样的系统必须是适用的。

2. Automated Analytical Procedures

The use of automated analytical procedures, although desirable for control testing, may lead to delay i

n regulatory methods validation because FDA laboratories have to assemble and validate the system before ru

nning samples. To avoid this delay, applicants should demonstrate the equivalence of a manual procedure to

the automated procedure based on the same principle whenever possible.

2. 自动分析方法

自动分析方法的使用会导致官方分析方法验证的延误，即使是非常适用于检测控制的，因为在样品分析之前，FDA 实验室必须要对系统进行装配和验证。为了避免这类延误，申请者应当尽可能论证在相同的原理基础上，手动分析方法和该自动分析方法是相当的。

ATTACHMENT A

NDA, ANDA, BLA, AND PLA SUBMISSION CONTENTS

The information relating to analytical procedures and methods validation that should be submitted in

NDAs, ANDAs, BLAs, and PLAs is identified below with a cross-reference to the section of this

guidance that provides recommendations and/or discussion on the topics.

Information that should be included in the analytical procedures and controls sections

! Reference standard information Section IV

- Analytical procedures Section III, VI
- Validation data Section VII
- Stress studies Section VII.A.2.c

- Instrument output/raw data for impurities Section VII.A.2.b
- Statistical analysis Section VIII
- Revalidation, as needed Section IX

附录A NDA, ANDA, BLA 和PLA申请的内容

需在 NDA，ANDA，BLA 和 PLA 中递交的分析方法和方法验证相关资料如下所示。并标明了本指南中给出了相应建议和/或讨论的章节的章节号。

在*分析方法和控制* 一章中需包括的资料

标准品信息	第 IV 章
分析方法	第 III，VI 章
分析方法验证资料	第 VII 章
强降解实验	第 VII.A.2.C 章
杂质研究的仪器输出/原始资料	第 VII.A.2.b 章
统计分析	第 VIII 章
必要的重验证	第 IX 章

Information that should be included in the methods validation package5

- Contents of the MV Package Section XI
- Representative instrument output/data for stress studies Section VII.A.2.c

! Representative instrument output and raw data for initial

and oldest sample of a batch Section VII.A.2.b

分析方法验证中所需包括的资料。

分析方法验证的内容	第 XI 章
强降解实验的代表性仪器输出/原始资料	第 VII.A.2.C 章
某一批次最初样品和最老样品的代表性仪器输出/	第 VII.A.2.b 章
原始资料	

Information that should be included in the stability section

! Stress study designs and results Section VII.A.2.b

! Reference (volume and page number of submission)

to instrument output and raw data submitted to the section

dedicated to analytical procedures and controls Section VII.A 2.c

稳定性章节中所需包括的资料。

强降解实验的实验设计和实验结果　　第 VII.A.2.b 章

参考分析方法和控制章节 中所递交的的代表性　　第 VII.A.2.C 章

仪器输出/原始资料

ATTACHMENT B

METHODS VALIDATION PROBLEMS AND DELAY

Listed below are examples of common problems that can delay successful validation.

! Failure to provide a sample of a critical impurity, degradation product, internal standard, or novel reagent

! Failure to submit well-characterized reference standards for noncompendial drugs

! Failure to provide sufficient detail or use of unacceptable analytical procedures. For example:

附录B 析方法验证的问题和延误

下文举列说明了些会延误成功验证的常见问题。

未能提供关键杂质，降解物，内标物或新试剂的样品。

未能提供非药典药物的已界定标准品。

未能提供分析方法的详细描述，或使用和了不可接受的分析方法。比如：

C Use of arbitrary arithmetic corrections

C Failure to provide system suitability tests

C Differing content uniformity and assay analytical procedures without showing

equivalence factors for defining corrections as required by the current USP chapter

<905> - Uniformity of Dosage Units

! Failure to submit complete or legible data. For example:

C Failure to label instrument output to indicate sample identity

C Failure to label the axes

随意使用数学校正。

未能提供系统适应性实验。

含量均一性分析和含量分析的分析方法是不一样的，且未说明校正用的等效因子，而这是美国药典*第<905>章：剂型的均一性* 所必需的。

未能提供完整清晰的数据。比如：

未能标注仪器输出。

未能标注坐标。

Inappropriate shipping procedures. For example:

C Failure to properly label samples

C Failure to package samples in accordance with product storage conditions

C Inadequate shipping forms (e.g., missing customs form for samples from outside the United States)

! Failure to describe proper storage conditions on shipping containers

不合理的运送方式。比如：

未能正确标注样品

未能根据产品储存条件来包装产品。

运单不完整(比如，没有国外样品的报关单)

未在运送包装上标明适当的储存条件。

GLOSSARY

Acceptance Criteria: Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures.

Active moiety: The molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance (21 CFR 314.108(a)). The active moiety is the entire molecule or ion, not the active site.

Detection Limit: The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample that can be detected, but not necessarily quantitated as an exact value.

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术语表

合格标准(Acceptance criteria)：分析结果的可接受数值限度，范围。

活性成分(Active moiety)：原料药中那些能起生理作用或药理作用的分子或离子，不包括那些使该药物分子成为酯，盐(包括带氢或配位键的盐)，或其它非共价键衍生物(比如，络合物，螯合物，或包合物)(21CFR 314.108(a))．活性成分指的是整个分子或离子，而不是*活性位置*。

检测限(Detection limit)：分析方法的检测限指的是样品中被分析物能被检测出的最低量，但并不需要定量检测。

Drug Product: A finished dosage form, for example, a tablet, capsule, or solution that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients (21 CFR 314.3(b)).

Drug Substance/Active Ingredient: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any *function* of the human body. The active ingredient does not include intermediates used in the synthesis of such ingredient. The term includes those components that may

undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect (21 CFR 210.3(b)(7) and 314.3(b)).

制剂(Drug product)：成品剂型，比如，片剂，胶囊，或包含某一原料药成分的溶液，通常还会有其它的一些组分，但这也不是必须的。(21 CFR 314.3(b))。

原料药/活性成分(Drug substance/active ingredient)：能在疾病的诊断，治疗上，缓解，处理或预防中起到药理作用或其它直接作用的成分，也包括能影响人体的结构和功能的成分。

原料药不包括那些在该原料药的合成过程中所用到的中间体。这个术语还包括那些在制剂生

产过程中为产生化学变化的的组分，或以改变后的形式存在的制剂中以完成某一功能或作用

的成分。(21 CFR 210.3(b)(7)和 314.3(b))。

Placebo (or Blank): A dosage form that is identical to the drug product except that the drug substance is absent or replaced by an inert ingredient or a mixture of the drug product excipients quantitatively equivalent to those found in the drug product dosage form.

Quantitation Limit: The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample that can be quantitatively determined with suitable precision and accuracy. The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products.

空白(Placebo or blank)：指不含活性成分，或用惰性成分代替了活性成分，而其它成分均与某一制剂保持一致的剂型。

定量限(Quantitation limit)：分析方法的定量限指的是样品中的被分析物可在适当的精密度和准确度下被定量检测出的最低量。检测量是低含量组分样品定量分析的一个参数，特别是用于杂质和/或降解物的测定。

Reagent: For analytical procedures, any substance used in a reaction for the purpose of detecting, measuring, examining, or analyzing other substances.

Specification: The quality standards (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of the drug substances, drug products, intermediates, raw materials, reagents, and other components including container closure systems, and

in-process materials.

试剂(Reagent)：在分析方法中用于检测，测量，检查或分析其它物质的物质。

规格(specification)：质量标准(也就是，检测项，分析方法和合格标准)，提供在已批准的申请中以确认原料药，制剂，中间体，原辅料，试剂和其它组分，包括容器密闭系统，和过程控制物料的质量。

Spiking: The addition of a small known amount of a known compound to a standard, sample, or placebo, typically for the purpose of confirming the performance of an analytical procedure or the calibration of an instrument.

Stability-Indicating Assay: A validated quantitative analytical procedure that can detect the changes with time in the pertinent properties (e.g., active ingredient, preservative level) of the drug substance and drug product. A stability-indicating assay accurately measures the active ingredients without interference from degradation products, process impurities, excipients, or other potential impurities.

Working Standard: A standard that is qualified against and used instead of the reference standard (also known as in-house or secondary standard).

加样(Spiking)：往标准，样品或空白中加入少量已知量的已知物，特别是用于确认某一分析方法的性能或对仪器进行校准。

稳定性指示分析(Stability-indicating assay)：可以检测出原料药和制剂的相关属性(如，活性成分，防腐剂的量）随着时间延长而产生的变化。稳定性指示分析能不受降解物，工艺杂质，•赋形剂或其它潜在杂质的影响对活性成分进行测定。

工作对照品(Working standard)：根据一级标准品进行确认的对照品，并用以代替一级对照品。(也被称之为内部对照品或工作对照品)。