化学药品与生物制品的分析程序与方法验证

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中英文对照版

目录

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I 简介

这个指南将取代在 2014 年 2 月 19 日发布的同名草案(79 FR 9467)，还代替了行业 2000 年关于分析方法和方法验证的草案，以及代替了 1987 年的提交样品和分析数据的方法验证指南。该草案提供了有关申请人如何提交分析程序和方法验证数据来支持说明原料药和制剂具有成分、强度、质量、纯度和效用的文件。它会帮你收集信息和现有数据来支持你的分析方法。该指导原则适用于原料药和制剂产品涵盖新药申请（NDA），简化新药申请（仿制药），生物制品许可申请（BLA），以及这些申请的补充申请。在这个修订草案指导原则也适用于原料药和制剂产品涵盖二类药物主文件（DMFs）。

该修订指南草案补充了国际协调会议（ICH）Q2（R1）指导原则《分析程序的验证：开发和验证的分析方法 Q2（R1）和方法的文本。

该修订指南草案不涉及研究性新药申请（IND）方法验证，但研究者在准备研究性新药申请时应考虑该指导原则中的建议。研究性新药申请需要在研究的每个阶段有足够的信息，以确保正确鉴别性，质量，纯度，强度和/或效力。对分析方法和方法验证的信息量将随研究中不同阶段而变化。一般来说，指南中的分析方法和方法验证信息会被提交给第一阶段研究，发起人应参照 FDA 指导中的对新药研究申请第一阶段药物研究的有关内容和格式，包括良好性能、治疗、生物技术衍生产品。对新药研究申请第二和第三阶段的药物研究中对分析方法和方法验证的讨论一般应考虑在第二和第三阶段研究之前，应参考 FDA 行业指导原则《人类药物和生物制剂、化学、制造、控制信息会议》。

该指南不涉及生物和免疫化学检测的表征和许多原料药和制剂产品质量控制的具体方法验证的建议。例如，一些基于动物模型的生物测定，并且免疫原性评估或其它免疫测定具有独特的特征，应开发和验证过程中予以考虑。

在产品和进程开发活动中所需要的分析方法在 FDA 的工艺验证：一般原则和实践中已被讨论了。另外，一种以风险为基础的方法应当被考虑到，在产品的生命周期内因生产工艺变化了而需要对现有的分析方法再验证。有关适当的验证方法的分析程序或者提交本指南中未提及的信息的问题，您应该向用 FDA 产品质量评审人员咨询。

如果您选择了与本指导草案中不同的方式，我们建议您在提交申请前与相应的 FDA 产品质量评审人员讨论。

FDA 的指南文件，包括本指导原则，不具有法律强制性的责任。相反，指南描述的是 FDA 对某个主题目前的想法，并应仅作为建议，除非有明确的法律或法规要求的引用。使用“应该”这个词在 FDA 指南意味着什么建议或推荐，但不是必需的。

II 背景

每个新药研究申请和仿制药申请应当包含分析程序，必须确保原料和制剂的成分、强度、质量、纯度和效力。每个 BLA 应当包含一个对生产过程完整的描述，包括分析程序去证明所制造的产品的成分、质量、安全、纯度和效力符合规定的标准。数据必须是可用的以确定在测试中使用的分析程序符合适当标准的准确性、灵敏度、特异性和重现性，并适合其预定的目的。

分析程序验证或验证数据应参照 ICHM2 eCTD（电子公共技术文档规范）申请中相应的部分提交。

当一个分析程序被批准/许可作为新药研究申请、仿制药研究申请或 BLA 的一部分，它成为 FDA 批准的产品的分析程序。这个分析程序可能来源于 FDA 认可的来源（如美国药典的/国家药典的药典方法或你提交的被 FDA 认可的验证程序）。给不同药物产品申请一个验证方法，应当考虑对新产品模型用药典方法进行适当的验证或验证研究。

III 分析方法开发

分析方法的开发是为了一个定义药物原料药与制剂产品特性的检测标准。新方法开发初期，应当基于分析项目与方法适用范围选择检测仪器和检测方法。该方法可在开发过程中进行专属性，线性，检测限（LOD）和定量限（LOQ），范围，精度和准确度的评估。

在方法开发过程的早期阶段，方法的稳定性应进行评估，因为这个特性可以帮助您确定哪一种方法您将提交审批。在发展的早期阶段分析程序最初开发基于基本方法和以往的经验机理认识的结合。早期程序的实验数据可用于指导进一步发展。你应该在方法验证部分中提交支持该方法的有效性的进一步支持数据。

要充分认识分析过程中方法参数改变的影响，你应该采取的方法的稳定性研究（例如，实验方法参数设计）的系统方法。你应该从风险评估开始，并跟进多因素实验。这些方法能让你了解到方法性能参数因子的影响。检测方法的性能评价贯穿了样品生产的整个过程。这些对分析方法起源的研究中获得的知识能帮助你评估方法的性能。

IV.分析程序内容

你应该尽可能详细地描述分析过程，让一个有能力的分析师去重现必要条件，并提出验收标准范围内得到结果。你还应该描述需要特别注意的分析程序方面的问题。一种分析方法可从 FDA 认可的资源中引用来（如美国药典/国家药典，国际分析社区协会），如果所参考的分析方法未经过修改超出了已发布方法的允许，你应提供详细的从其他出版来源的程序。你的一个分析过程应该包括下面这些必要的信息列表：

A：原则，范围

分析测试/技术（分离，检测等）的基本原理的说明;目标分析物和样品类型（如，药物，药品，生物体液等杂质或化合物）。

B：仪器，设备

所需要的合格的设备和零件（如仪器类型，检测器，柱子类型，尺寸，过滤器类型等）。

C. 操作参数

合格的最佳设置和范围（可予以调整）对分析至关重要（比如，流速，组件的温度，运行时间，顶空进样器、检测器的设置）。如果适用实验配置和集成参数的绘图也可以使用。

D. 试剂/标准

以下列出了适用的问题：

- 化学的等级（例如，USP / NF，美国化学学会，高效液相色谱级，或气相色谱级）。
- 来源（例如，参照美国药典标准或合格的内部参考材料）。
- 纯度（只针对化学纯），状态（如干燥的，未干燥的），和浓度
- 效能（CFR，USP 所要求的）
- 贮藏条件
- 安全使用说明书（按最新的安全数据）
- 经验证的保质期
- 新批次的生物试剂，例如单克隆抗体、多克隆抗血清、细胞等，可能需要包括更大范围的鉴定程序，作为分析程序的组成部分。

E. 样品制备

单次检测用样品制备程序（例如，提取方法、稀释或浓缩、脱盐程序以及超声混合、震动或超声处理时间等）。定性检测需要制备单份样品，定量检测需要制备双份样品，且工作溶液应使用合适的浓度单位（例如，µg/ml 或 mg/ml）；提供溶液稳定性和储存条件方面的相关信息。

F. 标准品对照溶液制备

带有合适浓度单位的所有标准品和对照溶液的制备和使用程序，标准品稳定性和储存条件相关信息，包括校验标准、内控标准、系统适用性等。

G. 程序

对分析方法进行逐步描述（例如，平衡时间，以及使用空白、安慰剂、样品、对照品、敏感溶液（杂质检测法用）和标准品进行扫描/注射的顺序，以维持检测期间系统适用性的有效性），以及允许的操作区间和调试（如适用）。

H．系统适用性

通过确认测试程序和参数，保证在系统（仪器设备、电子系统、分析操作以及用于分析的对照品）使用时，能够正常发挥整合系统的功能。在某些情况下，可能需要提供适用于标准品、对照品和样品的系统适用性可接受标准，例如峰拖尾、精密度和分辨率可接受标准。关于色谱系统的系统适用性，请参考 FDA 行业指南：《色谱方法验证》，以及《美国药典》通则<621>“色谱法”。

I． 计算

整合方法和用于数据分析（标准品、对照品、样品）的代表性计算公式，应基于药品标签和规格设定（例如，检测方法、规定和未规定的杂质、相对响应因子）。上述内容应当包括在数据分析过程中使用的任何数学转换以及公式；如果在计算过程中使用了校正因子，应当提供科学的理由。

J．数据报告

展示符合设备能力和可接受标准的数值型数据。分析方法应当说明使用何种格式报告结果（例如，标示量的百分比、质量/质量、质量/体积等），并规定有效数字的保留位数。美国试验材料协会（ASTM）标准 E29 提供了一种用于确认分析结果与质量标准之间的一致性时，检验结果有效数字保留位数的标准规范。对于色谱法，用于鉴别试验时应当在与参考标准品进行比较的基础上包括保留时间（RTs），以及相对保留时间（RRTs）（已知和未知杂质）可接受范围和样品结果报告标准。

V．参考标准品和材料

在 ICH 指南中对一级和二级参考标准品及材料进行了定义和讨论，详见 Q6B 标准：“生物技术产品/生物制品检测程序和可接受标准”，以及 Q7“原料药生产质量管理规范”。对于所有的标准品，应当保证使用的适用性。应当严格遵守参考标准品储存和使用条件以及处理指导之规定，避免变动和污染，进而避免引入额外杂质并导致分析结果不准确。对于计划在程序中使用的任何参考标准品和材

料，都应当提供相关的支持性信息。如果条件允许，参考标准品和材料的支持性信息应当包括合格检测报告和分析证书（包括稳定性方案、报告，以及相关已知杂质的情况）。对于 BLA（FDA 生物制品许可申请）下的生物制品，在年度报告中应当包括参考标准品后续批次的合格证。

参考标准品通常可以通过美国药典获得，也可以通过欧洲药典、日本药典、世界卫生组织、或美国国家标准与技术局获得。多个生物制品的参考标准品也可以通过 CBER（FDA 生物制品评价与研究中心）获得。对于在美国上市的某些生物制品，在上市销售之前，必须采用经 CBER 批准的参考标准品。其他来源的参考材料，应当按照 ICH 6B 要求，采用常规和超常规放行检测。参考材料的检测应当考虑使用正交法。其他检测可以包括用于确定参考材料适用性、而在药品或产品放行检测中不一定进行检测的属性（例如，更大范围的结构一致性，以及用于效价、纯度和杂质检测的正交技术）。应当按照现行参考品标准，对一批新的参考标准材料（正式或内部材料）进行确认/校准。对于生物参考标准品和材料，我们建议在确认新参考标准品时应遵循双重方法，以避免质量属性发生漂移。双重方法涉及对每一个新的参考标准品与一级参考标准品进行比较，使其与临床试验材料和当前的生产工艺产生联系。

VI. 分析方法验证

A. 非药典收录的分析程序

分析方法验证，是证明一个分析程序能够实现其预期使用目的的过程。在启动验证研究之前，应当明确定义并充分理解该分析程序的方法及目标。这种理解，应当通过以科学为基础的方法开发和优化研究而获得。验证数据产生的前提，应当是使用合格的仪器设备，按照经发起人批准的方案执行验证工作，且该方案应符合现行版 GMP 规定，并描述每一个验证子项的方法学原理以及预先设定的、合理的可接受标准。药品、药物成分和产品分析物分析方法验证方案或混合分析物分析方法验证方案应当分别按各自矩阵制定并执行。在您的申请中，应当包括验证研究的详细信息及结果。

B. 验证项目

尽管并非所有的验证项目都适用于所有类型的检测，但典型的验证项目如下：

特异性

线性

准确性

精密度（可重复性，中间精密度，可再现性）

范围

定量限

检测限

ICH Q2（R1）被认为是在分析方法验证项目的建议与定义方面的主要参考标准。也可以参考 FDA 行业指南“色谱方法验证”。

如果某程序是经过验证的定量分析程序，且能够检测药品储存期间质量属性的变化，则该检测属于稳定性指示检测。为了证明稳定性指示检测的特异性，应当进行组合挑战测试。某些挑战包括使用加入目标分析物和全部已知干扰物质的样品；经过多种实验室压力条件处理的样品；生产完成后储存时间较长的真实产品样品（通过最终生产工艺生产获得），或在加速温湿度条件下储存的真实产品样品。

作为 NDA、ANDA 或 BLA 的持有者，您必须：（1）提交数据，证明所使用的分析程序满足准确性和可靠性的相关标准，并且（2）在申请经批准后，如果任一条件发生变更，且该变更超出申请时提供的变更范围，则应当就每单变更通知 FDA，包括分析程序变更以及其他已建立的对照品的变更等。

提交的数据应当包括分析方法的稳健性评估数据，这部分工作通常在方法开发阶段进行，或作为计划性验证研究的一部分。

C．药典收录的分析程序

分析方法（例如，USP/NF，AOAC 国际官方分析方法，或其他公认的标准参考）的适用性应当在实际使用条件下进行确认。提交资料中应当包括用于证明 USP/NF 分析程序适用于药品或药物成分检验的信息，且上述证明信息应当通过确认方案产生。

确认方案的内容应当包括，但不限于：

（1）需要进行确认的药典分析方法，且包含预先确定的可接受标准；

（2）分析方法详述（例如，试剂的适用性、设备、组分、色谱条件、色谱柱、检测器类型、检测器信号响应灵敏度、系统适用性、样品制备和稳定性等）。在程序和确认范围中，应当说明在方案中需包含哪些验证项目（例如，特异性、检测限、定量限、精密度、准确性）。决定在方案中应当包含哪些验证/确认项目，取决于多方面因素，例如规格限度的设定是否比药典可接受标准更加严格，药物合成路径不同、生产工艺差异或药物基质不同而导致色谱法 RT 或 RRT 发生变化。如果遵循药典分析方法且不存在偏差，则不需要对药典方法进行稳健性研究。

VII. 统计分析与模型

A. 统计

通过对验证数据进行统计分析，可对照预先设定的可接受标准对验证项目进行评估。所有用于数据分析的统计程序和参数，都应当基于可靠的原理且满足预期评估需要。有几种统计方法在验证项目评估方面比较有用，例如，用方差分析（ANOVA）评估回归分析 R（相关系数），R 方（测定系数）或线性回归用来测量线性。用于评估验证特征许多统计方法依赖于总体数据的正态性，重要的是需判定是否符合 rej 等假设检验。有许多技术，如直方图，正态性检验和概率图可用于评估观察到的分布。这些方法可能需要适当的转换数据，以更好地观察到数据是否符合正态分布或自由分布（非参数）。在开发新的测试方法、评估现有的测试方法或评估测量系统性能以及分析数据的解释和处理的其他一般信息时，应查询有关统计程序的资料，以供参考。数据分析中，应保证通过使用适当验证软件或独立验证的正确性。

B.模型

一些分析方法可能使用化学计量学和/或多变量模型。在开发这些模型时，应该包括在统计上足够数量的模型开发样本和可比样本进行模型范围的验证。合适的软件应被用于数据分析。模型的参数应该刻意改变，以测试模型稳定性。

VIII、分析程序生命周期管理

一旦分析过程（包括法定方法）被成功验证（或验证）和实施，该过程应当在产品的整个生命周期应遵循来不断保证它仍然适合用于其预期目的。方法的性能趋势分析应定期进行，以评估是否需要进行优化分析程序或对分析过程的整体或部分进行重新验证。如果某一分析方法在分析方法中规定的使用条件下反复调整，才能满足建立了系统适用性的要求，则该分析方法应重新评估、验证或修订。

在一个产品，新信息和风险评估的生命周期（例如，更好地了解产品 CQAs 或新杂质的认识）可以保证新的或替代性分析方法的开发和验证。保证产品质量时，新的技术可以允许更多的理解和/或信心。申请人应定期评估的产品的分析方法是否恰当，并考虑新的或替代方法。

在分析生命周期的变化时，应当对样品进行适当数量的留样，以便进行比较研究。留样数量应根据科学原理和风险评估确定。对于那些生产过程中敏感且易产生复杂变化的产品，留样样品是作对比的重要工具。在比较研究中使用的留样样品应包括具有代表性的临床试验材料样品和销售产品。

如果基于风险的评估或其他驱动导致分析过程改变或更换新的方法，或者如果该分析方法被转移到一个新的测试位点; 应考虑再验证，一个新的验证工作，分析方法比较研究，或两者的组合。在某些情况下，改变药物物质或药物产品的生产过程中也可能有必要对分析程序进行重新验证。这些另外的研究将在下面讨论。

A.再验证

在验证部分（第六部分）中描述的原则适用于重新验证。当分析方法发生变化（例如，在配方或制造过程中设备或试剂或的改变），应考虑所有的分析程序的全部或部分的再验证。在药物制造过程中制造工艺的变化，或引入新的药物产品制剂，可能会影响方法的性能的改变（例如，合成路线，发酵）。分析方法应进行重新验证。

重新验证可以确保该分析方法保持其重要的性能特性（例如，专属性，精确度，准确度，等等），且重新验证的程度取决于变化的性质。

B.分析方法的可比性研究

当提出了替换一个 FDA 批准的分析方法与另一种分析方法，或当所述的分析方法从一个实验室传递到另一典型产生的分析方法研究可比性请求。有关统计程序信息用于确定两种试验方法的等价性，适当的文献或文本应咨询。这些方案在下面讨论。

1. 替代分析方法

另一种分析方法是，你在地方 FDA 批准的分析程序使用的分析方法。对于 NDA 或 ANDA，你应该包括在应用程序的任何建议替代的分析方法。您必须包括的说明 20 步骤。经批准后，为 NDA 或 ANDA，或批准在 BLA 一个程序，但不包括在 FDA 的监管，增加，修改，或删除了替代分析方法，它提供的身份，实力同样或更高的保证，优质的材料，纯度，或效力被测试按批准的 21 应用程序描述的分析过程中，必须记录在未来的年度报告。

对于生物制品，在少数情况下，分析步骤可以包括在一个 FDA 规章。如果所需的分析方法是通过调节不论如何描述，以及你想使用另一种方法，则必须符合 21 CFR610.9 提交的替代方法进行审查和批准（一）。必须提出证据说明该变形例将提供的生物产品的安全性，纯度，效力和有效性等于或大于由在用于生物产品的一般标准或其他标准规定的方法或工艺提供的保证的保证“修改这些程序，需要在应用程序的审查，或在批准后补充 FDA 的批准。

你应该确定所使用的替代分析方法（如，放行，稳定性测试），并提供了其包容性，验证数据，以及美国食品药品管理局批准的分析方法比较数据的理由。您应该执行的分析方法比较研究，证明至少是：加上任何附加的控制措施，新方法相当于或优于设计用途的新的分析方法是不是更容易受到比原程序基体效应的原始方法。

如果新的进程相关的或与产品相关的变体或任何新的杂质被发现的新程序，测试对历史批次保留样品应被执行以证明由该方法检测出的变体/杂质的增加的结果灵敏度或新程序的选择性和不改变到过程相关的杂质造成的。

如果过程具有稳定性指示属性：

•适当的样品具有比较新方法和原始方法检测有关物质和降解产物的能力。

•进行比较的分析批次的数量应该具有统计学相关性和合理的预先建立的置信区间。

•等效，非劣效性或优越性的研究应该用适当的统计方法进行，以表明新的或修订的方法性能与原来的方法相当或比原来的方法更好。

•进行比较的产品测试的统计分析应加以鉴别。

•比较结果的偏置应该进行讨论并附带适当的说明。

2. 分析方法转移研究

分析方法转移通常是在一个内部转移协议下进行，内部转移协议列出详细的参数用于检验将应用到结果的预定验收标准。转移研究通常涉及两个或多个实验室或实验点（原始实验室和接收实验室）执行预先批准转移协议。始发和接收实验室需要使用大量的有代表性的实验样品（例如，同一批次的原料药或制剂产品）。

比较研究评估准确度和精密度，尤其是涉及到评估实验室间的变异性。转移分析过程也是一个稳定指示方法，强制降解样品或含相关产品相关的杂质的样品应在两个站点进行分析。USP 通则<1224>《分析程序转移》为该主题提供了相关指导。

C. NDA，ANDA，BLA 批准上市后变更报告

上市后改变分析程序需报告 FDA 并符合 21 CFR314.70 和 21 CFR601.12. FDA 行业指南《已批准 NDA 或 ANDA 的变更》和《已批准 NDA 或 ANDA 的变更；规格 - 使用执法自由裁量权的药典变化》针对 NDA 或 ANDA 不同种类的上市后变更的相应报告类别提供了附加信息。由 CDER 和 CBER 监管的 BLAs 上市后变更的相似信息来源于 FDA 指南《特定生物技术及制定合成生物制品的已批准申请的变更》。

IX FDA 方法验证

部分 NDA 或 ANDA 的审批流程，包括 FDA 实验室评估，以确定该分析方法是否适用于质量控制和监管目的。如果进行实验室评估，FDA 实验室需要你根据 FDA 实验室提供的清单提供详细的样品和

相应的试剂。这些可能包括产品样本，标准品，关键试剂，材料安全数据表和耗材。实验室结果和意见将在 FDA 实验室被转发到产品的质量评审员。

对于某些生物制品，许可申请的产品中代表性样品及使用同批次产品进行测试的结果总结应与生物许可申请同时提交。FDA 实验室将验证的方法的性能和您提交的结果。在生物许可申请预审会或者提交生物许可后，FDA 实验室会需要你提供标准品、对照品、试剂、物料安全数据表（MSDS）和耗材。

Analytical Procedures and Methods Validation for Drugs and Biologics Guidance for Industry[1]

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

I. INTRODUCTION

This guidance supersedes the draft of the same name that published on February 19, 2014 (79 FR 9467) and replaces the 2000 draft guidance for industry on *Analytical Procedures and Methods Validation*[2 3], and the 1987 *Guidelines for Submitting Samples and Anafytical Data for Methods Validation.* It provides recommendations on how you, the applicant, can submit analytical procedures[2] and methods validation[3] data to support the documentation of the identity, strength, quality, purity, and potency of drug substances and drug products.[4] It will help you assemble information and present data to support your 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), and supplements to these applications. The principles in this guidance also apply to drug substances and drug products covered in Type II drug master files (DMFs).

This guidance complements the International Conference on Harmonisation (ICH) guidance *Q2(R1) Validation of Analytical Procedures: Text and Methodology* (Q2(R1)) for developing and validating analytical methods.

This guidance does not address investigational new drug application (IND) methods validation, but sponsors preparing INDs should consider the recommendations in this guidance. For INDs, sufficient information is required at each phase of an investigation to ensure proper identity, quality, purity, strength, and/or potency. The amount of information on analytical procedures and methods suitability will vary with the phase of the investigation.[5] For general guidance on

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.
[2] *Analytical procedure* is interchangeable with a *method* or *test procedure.*
[3] Compendial methods are verified rather than validated as described in section VI, C.
[4] The terms *drug substance* and *drug product* are used in this guidance to refer to both human drugs and biologics.
[5] See 21 CFR 312.23(a)(7).

analytical procedures and methods validation information to be submitted for phase one 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.* General considerations for analytical procedures and methods validation before conduct of phase two and three studies are discussed in the FDA guidances for industry on *INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products (February 1999)* and *IND Meetings for Human Drugs and Biologics, Chemistry, Manufacturing, and Controls Information.*

This guidance does not address specific method validation recommendations for biological and immunochemical assays for characterization and quality control of many drug substances and drug products. For example, some bioassays are based on animal challenge models, and immunogenicity assessments or other immunoassays have unique features that should be considered during development and validation.

Analytical methods required during product and process development activities are discussed in FDA guidance for industry on *Process Validation: General Principles and Practices.*

In addition, a risk-based approach on the need for revalidation of existing analytical methods may need to be considered when the manufacturing process changes during the product's life cycle. For questions on appropriate validation approaches for analytical procedures or submission of information not addressed in this guidance, you should consult with the appropriate FDA quality assessment staff.

If you choose a different approach than those recommended in this guidance, we encourage you to discuss the matter with the appropriate FDA quality assessment staff before you submit your application.

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 guidances means that something is suggested or recommended, but not required.

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. Each BLA must include a full description of the manufacturing process, including analytical procedures that demonstrate the manufactured product meets prescribed standards of identity, quality, safety, purity, and potency.[6] Data must be available to establish that the analytical procedures used in testing meet proper standards of accuracy, sensitivity, specificity, and reproducibility and are suitable for their intended purpose.[7]

[6] See 21 CFR 601.2(a) and 601.2(c).
[7] See 21CFR 211.165(e) and 211.194(a)(2).

Analytical procedures verification or validation data should be submitted in the corresponding sections of the application in the ICH*M2 eCTD: Electronic Common Technical Document Specification*[8]

When an analytical procedure is approved/licensed as part of the NDA, ANDA, or BLA, it becomes the FDA-approved analytical procedure for the approved product. This analytical procedure may originate from FDA recognized sources (e.g., a compendial procedure from the *United States Pharmacopeia/National Formulary* (USP/NF)) or a validated procedure you submitted that was determined to be acceptable by FDA. To apply an analytical method to a different drug product, appropriate validation or verification studies for compendial procedures with the matrix of the new product should be considered.

III. ANALYTICAL METHODS DEVELOPMENT

An analytical procedure is developed to test a defined characteristic of the drug substance or drug product against established acceptance criteria for that characteristic. Early in the development of a new analytical procedure, the choice of analytical instrumentation and methodology should be selected based on the intended purpose and scope of the analytical method. Parameters that may be evaluated during method development are specificity, linearity, limits of detection (LOD) and limits of quantitation (LOQ), range, accuracy, and precision.

During early stages of method development, the robustness of methods should be evaluated because this characteristic can help you decide which method you will submit for approval. Analytical procedures in the early stages of development are initially developed based on a combination of mechanistic understanding of the basic methodology and prior experience. Experimental data from early procedures can be used to guide further development. You should submit development data within the method validation section if they support the validation of the method.

To fully understand the effect of changes in method parameters on an analytical procedure, you should adopt a systematic approach for a method robustness study (e.g., a design of experiments with method parameters). You should begin with an initial risk assessment and follow with multivariate experiments. Such approaches allow you to understand factorial parameter effects on method performance. Evaluation of a method's performance may include analyses of samples obtained from various stages of the manufacturing process from in-process to the finished product. Knowledge gained during these studies on the sources of method variation can help you assess the method performance.

[8] Sections as applicable in Module 3: 3.2.S and 3.2.P.

IV. CONTENT OF ANALYTICAL PROCEDURES

You should describe analytical procedures in sufficient detail to allow a competent analyst to reproduce the necessary conditions and obtain results within the proposed acceptance criteria. You should also describe aspects of the analytical procedures that require special attention. An analytical procedure may be referenced from FDA-recognized sources (e.g., USP/NF, Association of Analytical Communities (AOAC) International)[9] if the referenced analytical procedure is not modified beyond what is allowed in the published method. You should provide in detail procedures from other published sources. The following is a list of essential information you should include for an analytical procedure:

A. Principle/Scope

A description of the basic principles of the analytical test/technology (i.e., separation, detection); target analyte(s) and sample(s) type (e.g., drug substance, drug product, impurities or compounds in biological fluids).

B. Apparatus/Equipment

All required qualified equipment and components (e.g., instrument type, detector, column type, dimensions, and alternative column, filter type).

C. Operating Parameters

Qualified optimal settings and ranges (include allowed adjustments supported by compendial sources or development and/or validation studies) critical to the analysis (e.g., flow rate, components temperatures, run time, detector settings, gradient, head space sampler). A drawing with experimental configuration and integration parameters may be used, as applicable.

D. Reagents/Standards

The following should be listed where applicable:

- Description of reagent or standard
- Grade of chemical (e.g., USP/NF, American Chemical Society, High Performance or Pressure Liquid Chromatography, or Gas Chromatography and preservative-free)
- Source (e.g., USP reference standard, qualified in-house reference material, WHO International Standard/Reference Material, CBER standard)
- Purity (for pure chemicals only), State (e.g., dried, undried), and concentration
- Potencies (where required by CFR, USP)
- Storage conditions
- Directions for safe use (as per current Safety Data Sheet)
- Validated or documented shelf life

[9] See 21 CFR 211.194(a)(2).

New batches of biological reagents, such as monoclonal antibodies, polyclonal antisera, or cells, may need extensive qualification procedures included as part of the analytical procedure.

E. Sample Preparation

Procedures (e.g., extraction method, dilution or concentration, desalting procedures and mixing by sonication, shaking or sonication time) for the preparations for individual sample tests. A single preparation for qualitative and replicate preparations for quantitative tests with appropriate units of concentrations for working solutions (e.g., |ig/ml or mg/ml) and information on stability of solutions and storage conditions.

F. Standards Control Solution Preparation

Procedures for the preparation and use of all standard and control solutions with appropriate units of concentration and information on stability of standards and storage conditions, including calibration standards, internal standards, system suitability standards, etc.

G. Procedure

A step-by-step description of the method (e.g., equilibration times, and scan/injection sequence with blanks, placeboes, samples, controls, sensitivity solution (for impurity method) and standards to maintain validity of the system suitability during the span of analysis) and allowable operating ranges and adjustments if applicable.

H. System Suitability

Confirmatory test(s) procedures and parameters to ensure that the system (equipment, electronics, and analytical operations and controls to be analyzed) will function correctly as an integrated system at the time of use. The system suitability acceptance criteria applied to standards controls and samples, such as peak tailing, precision and resolution acceptance criteria, may be required as applicable. For system suitability of chromatographic systems, refer to the FDA guidance for industry on *Validation of Chromatographic Methods* and USP General Chapter <621> *Chromatography.*

I. Calculations

The integration method and representative calculation formulas for data analysis (standards, controls, samples) for tests based on label claim and specification (e.g., assay, specified and unspecified impurities and relative response factors). This includes a description of any mathematical transformations or formulas used in data analysis, along with a scientific justification for any correction factors used.

J. Data Reporting

A presentation of numeric data that is consistent with instrumental capabilities and acceptance criteria. The method should indicate what format to use to report results (e.g., percentage label claim, weight/weight, and weight/volume) with the specific number of significant figures needed. The American Society for Testing and Materials (ASTM) E29 standard describes a

standard practice for using significant digits in test data to determine conformance with specifications. For chromatographic methods, you should include retention times (RTs) for identification with reference standard comparison basis, relative retention times (RRTs) (known and unknown impurities) acceptable ranges and sample results reporting criteria.

V. REFERENCE STANDARDS AND MATERIALS

Primary and secondary reference standards and materials are defined and discussed in the following ICH guidances: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products,* and *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*. For all standards, you should ensure the suitability for use. You should strictly follow storage and usage conditions and handling instructions for reference standards to avoid modifications and contaminations, which could result in additional impurities and inaccurate analysis. You should include information supporting any reference standards and materials that you intend to use in the application. Information supporting reference standards and materials should include qualification test reports and certificates of analysis (including stability protocols, reports, and relevant known impurity profile information) as applicable. For biological products under BLAs, qualification of subsequent reference standard lots should be included in annual reports.

Reference standards can often be obtained from USP and may also be available through the European Pharmacopoeia, Japanese Pharmacopoeia, World Health Organization, or National Institute of Standards and Technology. Reference standards for a number of biological products are also available from CBER. For certain biological products marketed in the U.S., reference standards authorized by CBER must be used before the product can be released to the market.[10] Reference materials from other sources should be characterized by procedures including routine and beyond routine release testing as described in ICH Q6B. You should consider orthogonal methods for reference material characterization. Additional testing could include attributes to determine the suitability of the reference material not necessarily captured by the drug substance or product release tests (e.g., more extensive structural identity and orthogonal techniques for potency, purity and impurities).

A new batch of reference standard material (official or in-house) should be qualified/calibrated against the current reference standard. For biological reference standards and materials, we recommend that you follow a two-tiered approach when qualifying new reference standards to prevent drift in the quality attributes. A two-tiered approach involves a comparison of each new reference standard with a primary reference standard so that it is linked to clinical trial material and the current manufacturing process.

VI. ANALYTICAL METHOD VALIDATION

A. Noncompendial Analytical Procedures

Analytical method validation is the process of demonstrating that an analytical procedure is suitable for its intended purpose. The methodology and objective of the analytical procedures should be clearly defined and understood before initiating validation studies. This understanding

[10] See 21 CFR 610.20.

is obtained from scientifically-based method development and optimization studies. Validation data must be generated under a protocol approved by the sponsor following current good manufacturing practices with the description of methodology of each validation characteristic and predetermined and justified acceptance criteria, using qualified instrumentation.[11] Protocols for both drug substance and product analytes or mixture of analytes in respective matrices should be developed and executed. You should include details of the validation studies and results with your application.

B. Validation Characteristics

Although not all of the validation characteristics are applicable for all types of tests, typical validation characteristics are:

- Specificity
- Linearity
- Accuracy
- Precision (repeatability, intermediate precision, and reproducibility)
- Range
- Quantitation limit
- Detection limit

ICH Q2(R1) is considered the primary reference for recommendations and definitions on validation characteristics for analytical procedures. The FDA guidance for industry on *Validation of Chromatographic Methods* is available as well.

If a procedure is a validated quantitative analytical procedure that can detect changes in a quality attribute(s) of the drug substance and drug product during storage, it is considered a stability-indicating test. To demonstrate specificity of a stability-indicating test, a combination of challenges should be performed. Some challenges include the use of samples spiked with target analytes and all known interferences; samples that have undergone various laboratory stress conditions; and actual product samples (produced by the final manufacturing process) that are either aged or have been stored under accelerated temperature and humidity conditions.

As the holder of the NDA, ANDA, or BLA, you must: (1) submit the data used to establish that the analytical procedures used in testing meet proper standards of accuracy and reliability, and (2) notify the FDA about each change in each condition established in an approved application beyond the variations already provided for in the application, including changes to analytical procedures and other established controls.[12]

The submitted data should include the results from the robustness evaluation of the method, which is typically conducted during method development or as part of a planned validation study.[13]

[11] For drugs see 21 CFR 211.165(e); 21 CFR 314.50 (d), and for biologics see 21 CFR 601.2(a), 601.2(c), and 601.12(a).
[12] For drugs see 21 CFR 314.50 (d), 314.70(d), and for biologics see 21 CFR 601.2(a), 601.2(c), and 601.12(a). For a BLA, as discussed, you must obtain prior approval from FDA before implementing a change in analytical methods if those methods are specified in FDA regulations.
[13] See section III and ICH Q2(R1).

C. Compendial Analytical Procedures

The suitability of an analytical procedure (e.g., USP/NF, the Official Methods of Analysis of AOAC International, or other recognized standard references) should be verified under actual conditions of use. Information to demonstrate that USP/NF analytical procedures are suitable for the drug product or drug substance should be included in the submission and generated under a verification protocol.

The verification protocol should include, but is not limited to: (1) compendial methodology to be verified with predetermined acceptance criteria, and (2) details of the methodology (e.g., suitability of reagent(s), equipment, component(s), chromatographic conditions, column, detector type(s), sensitivity of detector signal response, system suitability, sample preparation and stability). The procedure and extent of verification should dictate which validation characteristic tests should be included in the protocol (e.g., specificity, LOD, LOQ, precision, accuracy). Considerations that may influence what characteristic tests should be in the protocol may depend on situations such as whether specification limits are set tighter than compendial acceptance criteria, or RT or RRT profiles are changing in chromatographic methods because of the synthetic route of drug substance or differences in manufacturing process or matrix of drug product. Robustness studies of compendial assays do not need to be included, if methods are followed without deviations.

VII. STATISTICAL ANALYSIS AND MODELS

A. Statistics

Statistical analysis of validation data can be used to evaluate validation characteristics against predetermined acceptance criteria. All statistical procedures and parameters used in the analysis of the data should be based on sound principles and appropriate for the intended evaluation. Several statistical methods are useful for assessing validation characteristics, for example, an analysis of variance (ANOVA) to assess regression analysis R (correlation coefficient) and R squared (coefficient of determination) or linear regression to measure linearity. Many statistical methods used for assessing validation characteristics rely on population normality, and it is important to determine whether or not to rej ect this assumption. There are many techniques, such as histograms, normality tests, and probability plots that can be used to evaluate the observed distribution. It may be appropriate to transform the data to better fit the normal distribution or apply distribution-free (nonparametric) approaches when the observed data are not normally distributed. Appropriate literature or text should be consulted for information on statistical procedures to use when developing new test methods, evaluating existing test methods or evaluating measurement system performance, as well as other general information on the interpretation and treatment of analytical data. The data analysis should be assured either by using appropriately validated software or independent verification for correctness.

B. Models

Some analytical methods might use chemometric and/or multivariate models. When developing

these models, the number of samples to provide adequate statistical power and range for model development and validation should be considered. Suitable software should be used for data analysis. Model parameters should be deliberately varied to test model robustness.

VIII. LIFE CYCLE MANAGEMENT OF ANALYTICAL PROCEDURES

Once an analytical procedure (including compendial methods) is successfully validated (or verified) and implemented, the procedure should be followed during the life cycle of the product to continually assure that it remains fit for its intended purpose. Trend analysis on method performance should be performed at regular intervals to evaluate the need to optimize the analytical procedure or to revalidate all or a part of the analytical procedure. If an analytical procedure can only meet the established system suitability requirements with repeated adjustments to the operating conditions stated in the analytical procedure, the analytical procedure should be reevaluated, revalidated, or amended, as appropriate.

Over the life cycle of a product, new information and risk assessments (e.g., a better understanding of product CQAs or awareness of a new impurity) may warrant the development and validation of a new or alternative analytical method. New technologies may allow for greater understanding and/or confidence when ensuring product quality. Applicants should periodically evaluate the appropriateness of a product's analytical methods and consider new or alternative methods.

In anticipation of life cycle changes in analytics, an appropriate number of retention samples should be maintained to allow for comparative studies. The number should be based on scientific principles and an assessment of risk. For complex products that are sensitive to manufacturing changes, reserve samples can be an important tool to make these comparisons. The retention samples used in comparative studies should include samples that represent marketed product and, when possible, pivotal clinical trial material.

If a risk-based evaluation or other drivers lead to changes in an analytical procedure or replacement with a new method or if the procedure is transferred to a new testing site; revalidation, a new validation exercise, an analytical method comparability study, or a combination of these exercises should be considered. In some cases, changes to the drug substance or drug product manufacturing process may also warrant analytical procedure revalidation. These additional studies are discussed below.

A. Revalidation

Principles described in the validation section (section VI) apply to revalidation. When a change is made to an analytical procedure (e.g., a change in a piece of equipment or reagent or because of a change in manufacturing process or formulation), revalidation of all or part of the analytical procedure should be considered. Analytical method revalidation may also be warranted because of manufacturing process changes, such as an alteration in the drug substance manufacturing process that could impact method performance (e.g., route of synthesis, fermentation) or introduction of a new drug product formulation.

You should revalidate to ensure that the analytical procedure maintains its critical performance characteristics (e.g., specificity, precision, accuracy). The degree of revalidation depends on the

nature of the change.

B. Analytical Method Comparability Studies

Analytical method comparability study requests are typically generated when you propose to substitute an FDA-approved analytical procedure with an alternative analytical procedure or when an analytical method is transferred from one laboratory to the other. For information on statistical procedures to use for determining equivalence of two test methods, appropriate literature or text should be consulted.[14] These scenarios are discussed below.

1. Alternative Analytical Procedures

An alternative analytical procedure is an analytical procedure that you use in place of the FDA-approved analytical procedure. For an NDA or ANDA, you should include any proposed alternate analytical procedures in the application. You must include a description of the procedure. After approval, for an NDA or ANDA, or for a procedure approved in a BLA but not included in an FDA regulation, the addition, revision, or deletion of an alternative analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, must be documented in the next annual report.

For biological products, in rare cases an analytical procedure may be included in an FDA regulation. If the analytical method required is described by a regulation, however, and you want to use an alternate method, you must submit the alternate method for review and approval according to 21 CFR 610.9(a). You must present evidence demonstrating that the modification will provide assurances of the safety, purity, potency, and effectiveness of the biological product equal to or greater than the assurances provided by the method or process specified in the general standards or additional standards for the biological product" Modification of such procedures requires FDA approval during application review or in a postapproval supplement.[15]

You should identify the use of the alternative analytical procedure (e.g., release, stability testing) and provide a rationale for its inclusion, validation data, and comparative data to the FDA-approved analytical procedure. You should perform an analytical method comparability study that demonstrates at a minimum that:

- The new method coupled with any additional control measures is equivalent or superior to the original method for the intended purpose.

- The new analytical procedure is not more susceptible to matrix effects than the original procedure.

If new process-related or product-related variants or any new impurities are discovered with the

[14] See References section for examples including USP General Chapter <1010> *Analytical Data - Interpretation and Treatment and ASTM E2935 Standard Practice for Conducting Equivalence Testing in Laboratory Applications.*
[15] See 21 CFR 610.9(b).

new procedure, testing on retention samples from historical batches should be performed to demonstrate that the variants/impurities detected by the new method are a result of an increase in the sensitivity or selectivity of the new procedure and not a result of a change to process-related impurities.

If the procedure has stability-indicating properties:

- Appropriate samples should be included that allow a comparison of the ability of the new and original method to detect relevant product variants and degradation species.
- The number of batches analyzed for comparison should provide sufficient statistical power.
- Equivalence, non-inferiority, or superiority studies should be performed with appropriate statistical methods to demonstrate that the new or revised methods performance is comparable or better than the original method. [16]
- The statistical analyses performed to compare product testing should be identified.
- All bias or differences between analytical procedures seen with comparative results should be discussed with an explanation, as appropriate.

2. Analytical Methods Transfer Studies

Analytical method transfer is typically managed under a transfer protocol that details the parameters to be evaluated in addition to the predetermined acceptance criteria that will be applied to the results. Transfer studies usually involve two or more laboratories or sites (originating lab and receiving labs) executing the preapproved transfer protocol. A sufficient number of representative test articles (e.g., same lot(s) of drug substance or drug product) are used by the originating and receiving laboratories. The comparative studies are performed to evaluate accuracy and precision, especially with regard to assessment of interlaboratory variability. In cases where the transferred analytical procedure is also a stability-indicating method, forced degradation samples or samples containing pertinent product-related impurities should be analyzed at both sites. The USP General Chapter <1224> *Transfer of Analytical Procedures* provides additional guidance on this topic.

C. Reporting Postmarketing Changes to an Approved NDA, ANDA, or BLA

Postmarketing changes to analytical procedures must be reported to the FDA in compliance with 21 CFR 314.70 or 21 CFR 601.12.[17] Additional information on the appropriate reporting category for various kinds of postapproval changes for NDAs and ANDAs is provided in the FDA guidance for industry on *Changes to an Approved NDA* or *ANDA* and *Changes to an Approved NDA or ANDA; Specifications - Use of Enforcement Discretion for Compendial Changes.* Similar information on postapproval changes to BLAs regulated by CDER and CBER is provided in the FDA guidance *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products.*

[16] ASTM E2935 – Standard Practice for Conducting Equivalence Testing in Laboratory Applications.
[17] As noted, for a product licensed under a BLA, if the change is to a procedure prescribed in FDA regulations that change must be approved by FDA pursuant to 21 CFR 610.9(b).

IX. FDA METHODS VERIFICATION

Part of the approval process for NDAs and ANDAs may include FDA laboratory assessment to determine whether the analytical procedures are acceptable for quality control and suitable for regulatory purposes.[18] If a laboratory assessment will be conducted, the FDA laboratory will send you a request that will detail what samples and supplies to send to the FDA laboratory. These could include product samples, standards, critical reagents, material safety data sheets, and supplies. Laboratory results and comments will be forwarded from the FDA laboratory to the product quality reviewer.

For certain biological products, samples representative of the product for licensure along with summaries of results of tests performed on the lots represented by these samples should be submitted with the BLA.[19] The FDA laboratory verifies the performance of the methods and the results you submit. During a pre-BLA meeting or after submission of the BLA, the FDA laboratory can send you a request to provide standards, controls, reagents, material safety data sheets, and supplies.

X. REFERENCES

Guidance for Industry

AND As: Impurities in Drug Products (November 2010)

AND As: Impurities in Drug Substances (July 2009)

Changes to an Approved NDA or ANDA (April 2004)

Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products (July 1997)

Changes to an Approved NDA or ANDA; Specifications - Use of Enforcement Discretion for Compendial Changes (November 2004)

Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products (November 1995)

IND Meetings for Human Drugs and Biologics, Chemistry Manufacturing and Controls Information (May 2001)

INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products (February 1999)

Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production (October 2006)

[18] See 21 CFR 314.50(e).
[19] See 21 CFR 601.2(a).

Process Validation: General Principles and Practices (January 2011)

Reviewer Guidance, Validation of Chromatographic Methods (November 1994)

Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances (November 1994)

[27] Draft guidances have been included for completeness only. As draft documents, they are not intended to be implemented until published in final form. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

Guidance for Industry: International Conference on Harmonization

Q1A(R2) Stability Testing of New Drug Substances and Products (November 2003)

Q1B Stability Testing: Photostability Testing of New Drug Substances and Products (May 1997)

Q1C Stability Testing for New Dosage Forms (May 1997)

Q2(R1) Validation of Analytical Procedures: Text and Methodology (March 1995, May 1997)

Q3A(R2) Impurities in New Drug Substances (June 2008)

Q3B(R2) Impurities in New Drug Products (August 2006)

Q3C Impurities: Residual Solvents (December 1997)

Q3C Tables and List (February 2012)

Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (July 1996)

Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (December 2000)

Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (August 1999)

Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (August 2001)

United States Pharmacopeia/National Formulary

General Chapter <621> Chromatography

General Chapter <1010> Analytical Data - Interpretation and Treatment

General Chapter <1224> Transfer of Analytical Procedures

General Chapter <1225> Validation of Compendial Procedures

General Chapter <1226> Verification of Compendial Procedures

General Notices and Requirements, Applying to Standards, Tests, Assays, and Other Specifications of the United States Pharmacopeia: 7. Test Results

Interpretation and Treatment of Analytical Data; USP Pharmacopeial Forum, United States Pharmacopeial Convention, Inc., Rockville MD: 1994, Volume 24, Number 5, pp. 7051 - 7056

Other

ASTM Standard, E29 - 2008 Standard Practice for Using Significant Digits in Test Data to Determine Conformance with Specifications, ASTM International, West Conshohocken, PA, (www.astm.org).

ASTM E1488 - Standard Guide for Statistical Procedures to use in Developing and Applying Test Methods, ASTM International, West Conshohocken, PA, (www.astm.org).

ASTM E2782 - Standard Guide for Measurement Systems Analysis (MSA), ASTM International, West Conshohocken, PA, (www.astm.org).

ASTM Standard, E2935 - 2013 Standard Practice for Conducting Equivalence Testing in Laboratory Applications, ASTM International, West Conshohocken, PA, (www.astm.org).

J.N. Miller and Miller, J.C., 2010, Statistics and Chemometrics for Analytical Chemistry, 6th edition, Pearson Education Canada.

Saunders, B.D. and R.G. Trapp, 2004, Basic and Clinical Biostatistics, 4th edition, Lange Medical Books/McGraw Hill.

[2] Sample submission is described in section IX, FDA Methods Verification.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[8] See 21 CFR 314.50(d)(1) and 314.94(a)(9)(i).

[17] See 21 CFR 211.194(a)(2) and USP General Chapter <1226> *Verification of Compendial Procedures.*

[18] See References section for examples including USP <1010> *Analytical Data - Interpretation and Treatment, ASTM E1488 Standard Guide for Statistical Procedures to Use in Developing and Applying Test Methods and ASTM E2782 Standard Guide for Measurement Systems Analysis.*

[20] See 21 CFR 314.50.

[21] See 21 CFR 314.70(d)(1), (d)(2)(vii). 314.81(b)(2), and 601.12(d)(vii).