PDATR57 （中文）生物技术产品的分析方法验证与转移

Analytical Method Validation and Transfer for Biotechnology Products

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This Technical Report (TR) provides risk-based guidance for Analytical Method Validation (AMV), which follows Analytical Method Development (AMD) or Analytical Method Qualification (AMQ), and contains risk-based guidance for other, related method lifecycle steps, such as Analytical Method Transfer (AMT).

本技术报告（TR）为分析方法验证（AMV）提供基于风险的指导，该方法遵循分析方法开发（AMD）或分析方法确认（AMQ），并包

含其他相关方法生命周期步骤的基于风险的指导，例如分析方法转移（AMT）。

The guidance provided here builds upon the International Conference on Harmonization (ICH) Q2 (R1) guidelines and includes additional considerations for analytical platform technology (APT) methods as well as the impact of stakeholder considerations, and essentially all modern quality expectations as recommended in the ICH Q8 (R2), Q9, and Q10 guidelines (1-4).

此处提供的指南建立在 ICH Q2(R1) 准则的基础上，并包括对分析平台技术（APT）方法的其他考量，利益相关方考虑的影响，以及在 ICH Q8 (R2) 、Q9 和 Q10 指南中推荐的所有现代质量期望。

Similar to the manufacturing process, an analytical method can also be considered to be a process. The validation strategy for analytical methods could therefore conceptually follow those of Process Validation (5). AMV can then be defined as the collection and evaluation of data, from the analytical method development stage throughout routine QC testing, which establishes scientific evidence that an analytical method is capable of consistently delivering accurate and reliable results.

与制造工艺类似，分析方法也可以被认为是一种工艺。因此分析方法的验证策略在概念上可以遵循“工艺验证”（5）。AMV 可以被定义为数据的收集与评估，从分析方法开发阶段到常规 QC 检验，其确立了分析方法能够持续提供准确和可靠结果的科学证据。

1.1 Scope and Purpose 范围与目的

This TR is to provide practical and strategic guidance to efficiently use historical data and knowledge to design suitable risk-based AMV studies, and set appropriate protocol acceptance criteria. The typical method lifecycle steps prior, during, and beyond the AMV studies are illustrated in Figure 1.1-1. The typical steps prior to validation, usually performed at early

pharmaceutical development stages, are included in this figure to show the dependency among early- and late-stage lifecycle steps. The AMV process begins with the validation readiness assessment and continues with the post-validation steps, maintenance (validation continuum), transfer(s), comparability, as they may apply to the continuous demonstration of analytical method suitability. The typical sequence of all prevalidation, validation and post-validation steps, as illustrated in the bottom half of Figure 1.1-1, is reflected in the sequence of sections in this TR. Instead of dealing in great detail with many possible exceptions and special considerations, this TR is intended to provide practical guidance to typical development processes and AMV studies.

本技术报告旨在提供切实可行的策略指导，有效利用历史数据和知识设计合适的基于风险的 AMV 研究，并制定适当的方案验收标准。图 1.1-1 说明了 AMV 研究前期、期间和后期的典型方法生命周期步骤。通常在早期药物开发阶段进行验证前的典型步骤，包括在该图中显示的生命周期步骤早期和晚期之间的依赖性。AMV 过程从验证准备评估开始，并继续进行后验证步骤、维护（验证连续性）、转移和对比研究，因为它们可能会应用于分析方法适用性的连续性证明。如图 1.1-1 下半部分所示，本技术报告中的章节反映了所有预验证、验证和后验证步骤的典型顺序。本技术报告旨在为典型的开发过程和 AMV 研究提供实用指导，而不是对许多可能的例外和特殊考虑进行详细解决。

The guidance presented in this TR applies to all biotechnological manufacturers and all contract development and manufacturing organizations. This TR does not provide specific guidance for the timing of AMV study execution with respect to the parallel product development lifecycle stages or guidance for analytical instrument qualification.

本技术报告所提供的指导适用于所有生物技术制造商和所有合同

开发与制造组织。本技术报告未提供关于产品开发生命周期阶段的AMV研究执行时间或分析仪器确认指南的具体指导。

It should be considered that various new analytical technologies and/or the use of Process Analytical Technology (PAT) methods may suggest some modification to the validation strategies presented here. Specific aspects for the validation of bioassays such as curve fitting models and statistical reference-to-sample parallelism requirements are not covered in this TR. Case-specific considerations for microbiological method validation such as statistical sampling and testing environment conditions are also not covered as they depend on the analytical methodology and the intended use.

应考虑各种新分析技术和/或过程分析技术（PAT）方法的使用可能对此处介绍的验证策略提出一些修改建议。本技术报告中不包括生物分析验证的特定方面，例如曲线拟合模型和统计参考样本并行性要求。微生物学方法验证的个案特定考虑要素（如统计抽样和测试环境条件）也未涵盖，因为它们取决于分析方法学和预期用途。

AMV studies are typically executed for future routine-use methods but may not be required for analytical methods used in support of pharmaceutical development (5). Figure 1.1-2 illustrates the two different analytical method lifecycle paths separated according to the intended use of a particular method.

The intended use of a particular method can be assessed early as part of the overall quality target product profile (QTPP) and a method should be selected accordingly. The intended use should be further considered when developing, qualifying and validating analytical methods. For example, measuring a critical quality attribute (CQA) or a critical process parameter (CPP) may require a more rigorous approach to the overall validation process. The intended use of a method can change during the

method and/or product lifecycle(s) due to a specification change or other reasons.

AMV 研究通常是针对未来常规使用的方法而执行的，但对于用于支持药物研发的分析方法可能不需要（5）。图 1.1-2 说明了根据特殊方法的预期用途而区分的两种不同分析方法生命周期路径。早期将特殊方法的预期用途作为整体目标产品质量概况（QTPP）的一部分进行评估，并相应选择一种方法。在开发、确认和验证分析方法时，应进一步考虑预期用途。例如，测量关键质量属性（CQA）和关键工艺参数（CPP）可能需要对整个验证过程采取更严格的方法。由于质量标准的改变或其他原因，方法的预期用途可以在方法和/或产品生命周期内改变。

Figure 1.1-1 Analytical Method Lifecycle Steps from Selection to Qualification or Validation 图 1.1-1 分析方法生命周期从选择到确认或验证的步骤

Figure 1.1-2 Example of a Method Lifecycle from the Identification of the Intended Use to Post-Validation Maintenance

图 1.1-2 从预期用途识别到后验证维护的分析方法生命周期示例

Acceptance Criteria 验收标准

Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical method validation that is satisfied to determine suitability of test method performance (6).

可接受分析方法验证结果的数值限度、范围或其他合适的测量值符合确定测试方法性能的适用性（6）。

Accuracy 准确性

An analytical procedure expresses the closeness of agreement between the value that is accepted either as a

conventional true value or an accepted reference value and the value found. This is sometimes termed trueness (1).

分析方法的准确性是指真实值或认可的参考值与测量值之间的相似程度。准确性有时也称为真实度（1）。

Analysis of Variance (ANOVA)　方差分析（ANOVA）

A general statistical approach to data analysis (i.e., comparison of means) in which the variation in a method's results is partitioned among explanatory factors in order to systematically assess factor influence and/or variance components.

数据分析的一般统计方法（即均值比较），其中方法结果的变化被划分在解释因素之中，为了系统地评估因子影响和/或方差分量。

Analyte　分析物

A specific chemical moiety being measured, which can be intact drug, biomolecule or its derivative, impurity, and/or excipients in a drug product (7). [Synonym: measurand]

指被测量的特定化学部分可以是药物产品中的完整药物，生物分子或其衍生物，杂质和/或赋形剂（7）。[同义词：被测量物]

Analytical Instrument Qualification (AIQ)　分析安装确认（AIQ）

The qualification of the analytical instrument(s) used as part of the analytical procedure.

分析仪器确认是分析方法的一部分。

Analytical Platform Technology (APT)　分析平台技术（APT）

An analytical method that is used for multiple products and/or types of sample matrix without modification of the procedure. Similar to compendial methods, an APT method may not require full validation for each new product or sample type.

用于多种产品和/或样品前体类型的分析方法，无需修改方法。与药典方法类似，APT 方法可能不需要对每种新产品或样品类型进行全面验证。

分析方法

That which is performed in order to obtain a reportable result. The procedure should describe in detail the steps necessary to perform the analytical test. This may include but is not limited to: the sample, the reference standard and the reagents preparations, use of the apparatus, generations of the calibration curve, use of the formulae for the calculation (1). [Synonym: Method, Assay]

为了获得可报告的结果所进行的一种分析方式，应详细描述每个分析检测所必需的步骤。它包括但不限于：样品、参比标准品和试剂的配制、仪器的使用、标准曲线的绘制、计算公式的运用等（1）。[同义词：方法、含量测定]

Bias 偏差

A systematic difference in a method that manifests itself as a deviation of the method mean from an expected value.

是指偏离预期值的均值方法本身的系统性误差。

Biological Activity 生物活性

Property that describes the specific ability or capacity of a product to achieve a defined biological effect (8).

产品达到规定生物效力的特有能力或含量的性质（8）。

Bioanalytical Test Method 生物分析测试方法

A method used to assess the presence of analytes (chemical or biological) in biological samples (e.g., serum, plasma, etc.) (7).

是指用于评估生物样品（例如，血清、血浆等）中分析物（化学或生物）的方法（7）。

Bioassay 生物分析

Analysis (as of a drug) to quantify the biological activity(ies) of one or more components by determining its capacity for producing an expected biological activity.

通过确定其产生预期生物活性的能力来分析（作为药物）量化一

Blocking 模块

The grouping of related experimental units used in design of experiments (DOE).

用于实验设计（DOE）的相关实验单元组。

Calibration Curve 校正曲线

The relationship between measured response values and analytical concentrations of a standard or reference material.

测量的响应值与标准品或对照品分析浓度之间的关系。

Coefficient of Determination (r2) 决定系数(r2)

A measure of the proportion of the variation of one variable determined by the variation of the other. 通过另一变量确定可变变量比例的量度。

Comparability, Method 分析方法对比研究

The demonstration of analytical method comparability (AMC) for method replacements.

证明替代方法的分析方法对比研究。

A study to demonstrate that a modification to an existing method either improves or does not significantly change the analytical procedure's characteristics relative to the methods' validation and intended use.

一项研究表明，对现有方法的修改可以改进或相对于方法验证和预期用途不会显著改变分析方法特性。

Compendial Procedure 药典方法

A method that is considered validated as published in one of the recognized compendia.

是指一种被认为在公认药典公布的已验证的方法。

Confidence Interval 置信区间

An interval estimate (range of values) of a population parameter, calculated from a random sample of the underlying

是指一个总体参数的区间估计值（数值的范围），从基础总体的随机样本计算得出。Correlation Coefficient (r)　　相关系数(r)

A measure of covariation, the square root of the coefficient of determination.

是指共变的量度，决定系数的平方根。

Co-Validation　联合验证

Sending and receiving laboratories participate in the AMV study execution.

转出和转入实验室共同参与执行 AMV 研究。

Critical Reagent　关键试剂

A component of the test method that may have a substantial impact on the consistency and reliability of method performance. Features of critical reagents include:

测试方法的组成部分，可能对方法性能的一致性和可靠性产生重大影响。关键试剂的特点包括：

1. A reagent that requires qualification of each new batch prior to routine use in an analytical

procedure, or

分析方法常规使用之前需要对每一新批次进行确认的试剂，或

2. A material whose method performance characteristics may change over time, during handling,

or from lot to lot.

其方法性能特征可能随时间变化、处理期间变化或批次之间变化的物料。

3.An analytical reagent that may be purchased only from a single vendor.

仅从唯一供应商购买而得的分析试剂。

Reagent Examples: antibodies or enzymes that require titration prior to use, tissue culture treated plates when only one

r a bioassay, growth factors for bioassay cells, conjugated proteins that require custom preparations, or reference or system suitability standards.

试剂示例：在使用前需要滴定的抗体或酶；唯一供应商给出可接受生物分析结果的组织培养平板；生物分析细胞的生长因子；需要定制的结合蛋白；对照品或系统适用性标准品。

Degradation Product　　降解产物

Molecular variants resulting from changes in the desired product or product-related substance brought about over time and/or by the action of light, temperature, pH, water, etc., or by reaction with an excipient and/or the immediate container/closure system. Such changes may occur because of manufacture and/or storage (e.g., deamidation, oxidation, aggregation, proteolysis). Degradation products may be either product-related substance or product-related impurities (8).

是指预期产品或产品相关物质长时间放置和/或受光、温度、pH、水的作用，或与赋形剂和/或直接接触的容器/密闭系统发生反应而产生的分子变异体。在生产和/或贮存过程中也可能发生这些变化（如脱酰胺、氧化、凝集、蛋白水解）。降解产物可能是产品相关物质，也可能是产品相关杂质（8）。

Design of Experiments (DOE)　　实验设计(DOE)

A structured, organized method for determining the relationship between factors affecting an assay and output of that assay (2).

用于确定影响含量测定及测定结果因素之间关系的结构化的、有组织的方法（2）。

Design, Experimental　　设计，实验的

The arrangement of factors and factor levels. Optimal experimental design minimizes “noise” in data to allow focus on the influence on assay response of critical factors. A factorial

analytical purpose. (May be modified with complete block, factorial, fractional factorial, full factorial, incomplete block) (9).

因素和因素水平的安排。最佳的实验设计可以最大限度地减少数据中的“噪音”，以便集中关注对关键因素的含量分析响应的影响。一个因子变化的实验（DOE）可以最快达成分析目的所需的实验（可以用完整模块、因子、部分因子、全部因子和不完整模块来修改）（9）。

Drug Product 制剂

A pharmaceutical product type that contains a drug substance, generally, in association with excipients (8). [Synonym: Dosage Form; Finished Product]

通常是含有原料药并与赋形剂放在一起的一种药品类型（8）。[同义词：剂型；成品]

Drug Substance 原料药

The active ingredient that is subsequently formulated with excipients to produce the drug product. It can be composed of the desired product, product-related substances, and product- and process-related impurities. It may also contain excipients, including other components such as buffers (8). (Synonyms: bulk drug substance, bulk material)

是指与赋形剂制成制剂的活性成分。它由预期产品、产品相关物质、产品和工艺相关杂质组成。它也可能含有包括其他成分的赋形剂，如缓冲剂（8）。[同义词：散装原料药，散装物料]

Equivalence 等效性

A comparison with the primary objective of showing that the results from two methods differ by an amount which has negligible impact on fitness for use. This is usually demonstrated by showing that the true difference is likely to lie between a lower and an upper equivalence margin of acceptance differences (10).