ABSTRACT

The U.S. Food and Drug Administration (FDA) has published its long-awaited Guidance for Industry document "Analytical Procedures and Methods Validation for Drugs and Biologics." The purpose of the guidance is support of new drug applications and what types of data are needed for new drug applications. Sections in the document listed. Key changes are described. These include: Scope, length, risk assessment, new sections, immunoassay and bioassay; essential information, reference standards, re-validation, and method transfer. The new guidance offers a clear signal to the industry as the FDA expectations for analytical methods and data presentation in support of new drug applications.

INTRODUCTION

The U.S. Food and Drug Administration (FDA) has published its long-awaited Guidance for Industry document "Analytical Procedures and Methods Validation for Drugs and Biologics" (1). The revised guidance was published in July 2015 and it supersedes the draft of the same name that published on February 19, 2014 (2). The document is important for laboratory staff and pharmaceutical organizations to digest. It outlines the Agency’s recommendations for qualifying and running analytical methods. Moreover, there are several changes since the original version of the document was released fifteen years ago.

The purpose of the guidance is support of new drug applications and what types of data are needed for new drug applications. The document is concerned with the types of analytical methods used to assess the identity, strength, quality, purity, and potency of drug substances and drug products. This includes methods that support new drug applications and biologics license applications. Tests should be conducted and described in sufficient detail so that they can be reproduced in another laboratory by a different qualified analyst. The document also extends beyond the operation of the methods in considering how to select, interpret, and present data collected from analytical methods.
The new document is the FDA's third set of guidances in this subject area. The first appeared in 1987; the second in 2000; the third, although welcome, has taken far too long, especially given the pace in pharmaceutical laboratory technology. One beneficial outcome from the delay is that the document is now better aligned with guidance on the same topic from the International Conference on Harmonisation (ICH).

**CONTENT**

The guidance is an important one for industry. Key sections in the document, and where recommendations are made, are the following:

- Analytical methods development
- Content of analytical procedures
- Reference standards and materials
- Analytical method validation
- Statistical analysis and models
- Life cycle management of analytical procedures
- FDA methods verification

**KEY CHANGES**

1. **Scope.** In contrast to the 2000 version, the document states that its scope extends to biologics. This means that the requirements of the Guideline apply to new drug applications (NDAs), abbreviated new drug applications (ANDAs), biologics license applications (BLAs), and variation applications relating to these types of application, as well as to Type II Drug Master Files. The scope does not extend to investigational new drug applications (INDs).

2. **Length.** The second thing to note is that the guidance is much shorter than the 2000 version. There is less detail provided about ways to conduct testing and a list of recommended validation parameters no longer appears in the text. Care must be taken here for the reference section has been expanded considerably and FDA expects users to refer to some of these references for more detailed information in relation to key validation parameters.

3. **Risk.** In keeping with the change in Good Manufacturing Practices over the course of the twenty-first century, the FDA guidance places risk assessment at the centre of the analytical method approach. Here the Agency is being less prescriptive than in the past and is placing the “what and how to assess?” back with the user.

4. **New sections.** There are some new sections. The most important of these are sections 8 and 9. Section 8 is concerned with the life cycle management of analytical procedures and section 9 with the verification of procedures in FDA laboratories. This latter section provides an indication to how FDA itself goes about qualifying methods.
Regarding lifecycle, the guidance advises that analytical methods should be reviewed during the lifecycle of the product to see if they require revalidation. This might occur should a process parameter drift or be redefined. Another reason is with the method itself. The guidance recommends that the method is studied over time: “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.”

The change control process is an effective way to capture both process and methodological changes. Risk assessment is the recommended approach to determine if any such reassessment is necessary. If modification of a method cannot be attempted, then the guidance provides the basis for the substitution of a new method.

5.

**Immunoassay and Bioassay.** Although immunological and biological assays are now featured there is little in terms of their description. This is probably because of the range of different tests that these types of test cover, with many biological assays requiring complex animal models.

6.

**Essential Information.** The document provides advice on how an analytical method should be reported. This is in keeping with the point made above -- that the method should be able to be reproduced under the same conditions by a different analyst working in a different laboratory. To help with this the guidance outlines ten items of “essential information” that need to be included for an analytical procedure. These are:

- Principle/scope. A description of the basic principles of the analytical test/technology.
- Apparatus/equipment
- Operating parameters. Optimal settings and ranges critical to the analysis. For example instrument operating temperature or flow rate.
- Reagents/standards. Important things to include here are the description of the standard, its source, purity, potency, storage conditions, direction for use and shelf-life assessment.
- Sample preparation
- Standards Control Solution Preparation. This needs to include units of concentration and information on stability of the standards.
- Procedure. The procedure should be written in such a way so that it is reproducible.
- System Suitability. This refers to the array of tests necessary to demonstrate that the system (equipment, electronics, and analytical operations and controls to be analysed) will function correctly as an integrated system at the time of use.
- Calculations
- Data reporting.

The calculations and reporting sections make reference to appropriate methods for statistical analysis and models. Statistical tools listed include analysis of variance (ANOVA), R squared (coefficient of determination) and linear regression.
When a non-compendial method is to be used (one not described in the USP), the guidance describes what is required. Here data relating to the method validation must be produced under a protocol. The new drug application needs to contain detail about the validation study and provide the results. Results should be assessed in relation to the following assay characteristics: specificity, linearity, range, accuracy and detection limit. These are in keeping with ICH Q2 “Validation of Analytical Procedures: text and methodology” (3). For compendia methods verification, rather than validation, is required. This is necessary to demonstrate the method is appropriate across pre-determined acceptance criteria.

The essential thing in establishing the suitability of the method is to demonstrate that the method can detect changes in a quality attribute. There are different ways to approach this. One common example is the challenge the method by using samples spiked with target analytes and various interferences. To this can be added samples that have undergone various laboratory stress conditions; and product samples that are either aged naturally or which have been stored under accelerated temperature and humidity conditions.

7.

Reference Standards. The guidance describes the importance of reference standards. Where a new reference standard is introduced into a laboratory the guidance stipulates that a new batch of reference standard materials must be qualified against the current standards before being implemented. This is a key point because all information about any reference standards used must be included within the drug submission.

8.

Re-Validation. The guidance addresses the problematic issue of re-validation. When and how often to re-validate is something that the pharmaceutical industry has yet to define. The guidance indicates that when a change is made to an analytical procedure, such as a change in equipment or reagent, then re-validation of all or part of the analytical procedure needs to be considered. Such consideration should also be given in light of any manufacturing process changes. Method re-validation should focus on the critical performance characteristics of the method, such as specificity, precision, and accuracy. The scope of re-validation should be risk-based.

9.

Method Transfer. The final key point is a reference to the transfer of methods between laboratories. The guidance suggests that with transfer studies, a sufficient number of representative samples are used by both the originating and receiving laboratories to perform comparative studies. These studies should evaluate accuracy and precision, noting the extent of any inter-laboratory variability.

SUMMARY

The new guidance is welcome. It offers a clear signal to the industry as the FDA expectations for analytical methods and data presentation in support of new drug applications. While detailed, the document offers a framework that is less prescriptive. It allows the user to make some risk-based decisions on test requirements. For this process, the document cross references 21 CFR and other FDA documentation. It should serve the pharmaceutical sector well for the next few years.
REFERENCES


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