Analytical Procedures and Methods Validation for Drugs and Biologics

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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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guidance supersedes the draft of the same name that published on February 19, 2014 (79 FR 9467) and replaces the 2000 draft guidance for industry on *Analytical Procedures and Methods Validation*[2,3] and the 1987 *Guidelines for Submitting Samples and Analytical Data for Methods Validation*. It provides recommendations on how you, the applicant, can submit analytical procedures[4] and methods validation[5] data to support the documentation of the identity, strength, quality, purity, and potency of drug substances and drug products.[6] 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.[7] 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] 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.
[4] *Analytical procedure* is interchangeable with a *method* or *test procedure*.
[5] Compendial methods are verified rather than validated as described in section VI, C.
[6] The terms *drug substance* and *drug product* are used in this guidance to refer to both human drugs and biologics.
[7] 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.[8] 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.[9] Data must be available to establish that the analytical procedures used in

[8] See 21 CFR 314.50(d)(1) and 314.94(a)(9)(i).
[9] See 21 CFR 601.2(a) and 601.2(c).

testing meet proper standards of accuracy, sensitivity, specificity, and reproducibility and are suitable for their intended purpose.[10]

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*.[11]

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.

[10] See 21 CFR 211.165(e) and 211.194(a)(2).
[11] 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)[12] 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

[12] 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., µg/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.[13] 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

[13] See 21 CFR 610.20.

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 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.[14] 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.

[14] 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).

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.[15]

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.[16]

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.[17] 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

[15] 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.

[16] See section III and ICH Q2(R1).

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

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 reject 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.[18] 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.

[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.*

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.[19] 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.[20] 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,

[19] 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.*

[20] See 21 CFR 314.50.

or potency of the material being tested as the analytical procedure described in the approved application, must be documented in the next annual report.[21]

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.[22]

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 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. [23]
- The statistical analyses performed to compare product testing should be identified.

[21] See 21 CFR 314.70(d)(1), (d)(2)(vii). 314.81(b)(2), and 601.12(d)(vii).
[22] See 21 CFR 610.9(b).
[23] ASTM E2935 – Standard Practice for Conducting Equivalence Testing in Laboratory Applications.

- 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.[24] 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.*

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.[25] 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.[26] The FDA laboratory verifies the performance of the methods and the

[24] 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).
[25] See 21 CFR 314.50(e).
[26] See 21 CFR 601.2(a).

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.

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Guidance for Industry[27]

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[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)

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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)

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

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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

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