Guidance for Industry

Analytical Procedures and Methods Validation for Drugs and Biologics

DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) Lucinda Buhse 314-539-2134, or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 301-827-1800.

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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CMC

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Analytical Procedures and Methods Validation for Drugs and Biologics

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Phone: 301-796-3400; Fax: 301-847-8714
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Food and Drug Administration
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Analytical Procedures and Methods Validation for Drugs and Biologics

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This revised draft guidance supersedes the 2000 draft guidance for industry on *Analytical Procedures and Methods Validation*[2,3] and, when finalized, will also replace the 1987 FDA guidance for industry on *Submitting Samples and Analytical Data for Methods Validation*. It provides recommendations on how you, the applicant, can submit analytical procedures[4] and methods validation data to support the documentation of the identity, strength, quality, purity, and potency of drug substances and drug products.[5] 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 The principles in this revised draft guidance also apply to drug substances and drug products covered in Type II drug master files (DMFs).

This revised draft 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 revised draft 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 validation will vary with the phase of the investigation.[6] For general

[1] This guidance has been prepared by the Office of Pharmaceutical Science, 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] The terms *drug substance* and *drug product*, as used in this guidance, refer to human drugs and biologics.

[6] See 21 CFR 312.23(a)(7).

guidance on 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 method validation (e.g., bioassay) before conduct of phase three studies are discussed in the FDA guidance for industry on *IND Meetings for Human Drugs and Biologics, Chemistry, Manufacturing, and Controls Information*.

This revised draft 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.

In addition, 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 product quality review staff.

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

FDA's guidance documents, including this guidance, 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.[7] Each BLA must include a full description of the manufacturing methods, including analytical procedures that demonstrate the manufactured product meets prescribed standards of identity, quality, safety, purity, and potency.[8] Data must be available to establish that the analytical procedures used in testing meet proper standards of accuracy and reliability and are suitable for their intended purpose.[9] For BLAs and their supplements, the analytical procedures and their validation are submitted as part of license applications or supplements and are evaluated by FDA quality review groups.

[7] See 21 CFR 314.50(d)(1) and 314.94(a)(9)(i).
[8] See 21 CFR 601.2(a) and 601.2(c).
[9] See 21 CFR 211.165(e) and 211.194(a)(2).

Analytical procedures and validation data should be submitted in the corresponding sections of the application in the ICH *M2 eCTD: Electronic Common Technical Document Specification*.[10]

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 product, appropriate validation studies 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 quantitation limits (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 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 in-process manufacturing stages to the finished product. Knowledge gained during these studies on the sources of method variation can help you assess the method performance.

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,

[10] See sections 3.2.S.4 Control of Drug Substance, 3.2.P.4 Control of Excipients, and 3.2.P.5 Control of Drug Product.

Association of Analytical Communities (AOAC) International)[11] if the referenced analytical procedure is not modified beyond what is allowed in the published method. You should provide in detail the 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 (separation, detection, etc.); target analyte(s) and sample(s) type (e.g., drug substance, drug product, impurities or compounds in biological fluids, etc.).

B. Apparatus/Equipment

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

C. Operating Parameters

Qualified optimal settings and ranges (allowed adjustments) 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:

- 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 or qualified in-house reference material).
- State (e.g., dried, undried, etc.) and concentration.
- Standard potencies (purity correction factors).
- Storage controls.
- Directions for safe use (as per current Safety Data Sheet).
- Validated or useable shelf life.

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, etc.) for the preparations for individual sample tests. A single preparation for qualitative and replicate preparations for quantitative tests with

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

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 and controls, such as peak tailing, precision and resolution acceptance criteria, may be required as applicable. For system suitability of chromatographic systems, refer to CDER reviewer guidance 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 etc.) with the specific number of significant figures needed. The American Society for Testing and Materials (ASTM) E29 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: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (ICH Q6A), *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. Reference standards for drug substances are particularly critical in validating specificity for an identity test. You should strictly follow storage, usage conditions, and handling instructions for reference standards to avoid added impurities and inaccurate analysis. For biological products, you should include information supporting any reference standards and materials that you intend to use in the BLA and in subsequent annual reports for subsequent reference standard qualifications. Information supporting reference standards and materials include qualification test protocols, reports, and certificates of analysis (including stability protocols and relevant known impurity profile information, as applicable).

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.[12] Reference materials from other sources should be characterized by procedures including routine and beyond routine release testing as described in ICH Q6A. You should consider orthogonal methods. 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 purity and impurities, biological activity).

For biological reference standards and materials, we recommend that you follow a two-tiered approach when qualifying new reference standards to help prevent drift in the quality attributes and provide a long-term link to clinical trial material. A two-tiered approach involves a comparison of each new working 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 FOR NDA, ANDAs, BLAs, AND DMFs

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

[12] See 21 CFR 610.20.

is obtained from scientifically-based method development and optimization studies. Validation data must be generated under an protocol approved by the sponsor following current good manufacturing practices with the description of methodology of each characteristic test and predetermined and justified acceptance criteria, using qualified instrumentation operated under current good manufacturing practices conditions.[13] Protocols for both drug substance and product analytes or mixture of analytes in respective matrices should be developed and executed.

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

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

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 assay. To demonstrate specificity of a stability-indicating assay, 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:[14] (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.

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.[15]

[13] 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).
[14] 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 below, you must obtain prior approval from FDA before implementing a change in analytical methods if those methods are specified in FDA regulations
[15] See section III and ICH Q2(R1).

C. Compendial Analytical Procedures

The suitability of an analytical procedure (e.g., USP/NF, the AOAC International Book of Methods, or other recognized standard references) should be verified under actual conditions of use.[16] Compendial general chapters, which are complex and mention multiple steps and/or address multiple techniques, should be rationalized for the intended use and verified. 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, etc.). 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. Reportable statistics of linear regression analysis R (correlation coefficient), R square (coefficient of determination), slope, least square, analysis of variance (ANOVA), confidence intervals, etc., should be provided with justification. For information on statistical techniques used in making comparisons, as well as other general information on the interpretation and treatment of analytical data, appropriate literature or texts should be consulted.[17]

B. Models

Some analytical methods might use chemometric and/or multivariate models. When developing these models, you should include a statistically adequate number and range of samples for model development and comparable samples for model validation. Suitable software should be used for data analysis. Model parameters should be deliberately varied to test model robustness.

[16] See 21 CFR 211.194(a)(2) and USP General Chapter <1226> *Verification of Compendial Procedures.*
[17] See References section for examples including USP <1010> *Analytical Data – Interpretation and Treatment.*

VIII. LIFE CYCLE MANAGEMENT OF ANALYTICAL PROCEDURES

Once an analytical procedure (including compendial methods) is successfully validated and implemented, the procedure will be followed during the life cycle of the product. 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 (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 samples should be archived 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, archived samples can be an important tool to make these comparisons. The archived samples used in comparative studies should include samples that represent pivotal clinical trial material and marketed product.

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, etc). 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. 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.[18] 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.[19] Additions or revisions of analytical procedures in BLAs may require submission as a supplement. FDA recommends discussion with the appropriate review group to determine the appropriate reporting category

For biological products, rarely an analytical procedure may be included in an FDA regulation. When that occurs, alternative analytical procedures are submitted following 21 CFR 610.9(a). It states that the applicant will 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.[20]

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 a comparability study that demonstrates at a minimum that:

- The new method coupled with any additional control measures is equal or superior for 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 or product related variants or any new impurities are discovered with the new procedure, testing on archived 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

[18] See 21 CFR 314.50.
[19] See 21 CFR 314.70(d)(1), (d)(2)(vii). 314.81(b)(2), and 601.12(d)(vii).
[20] See 21 CFR 610.9(b).

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 be statistically relevant and justified for a pre-established confidence interval.
- Equivalence, non-inferiority, or superiority studies should be performed with appropriate statistical methods to demonstrate that the new or revised method performance is comparable or better than the original method.
- The statistical analyses performed to compare product testing should be identified.
- All bias seen with comparative results should be discussed with an explanation, as appropriate.

2. Analytical Methods Transfer Studies

Analytical method transfer is typically managed under an internal 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.[21] 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.*

[21] 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.[22] 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.[23] The FDA laboratory verifies the performance of the methods and the results you submit. During the 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[24]

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

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

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

[22] See 21 CFR 314.50(e).

[23] See 21 CFR 601.2(a).

[24] Draft guidances have been included for completeness only. As draft documents, they are not intended to be implemented until published in final form.

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

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General Chapter <1224> Transfer of Analytical Procedures

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

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