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"THE U.S. FDA REGULATORY METHODS VALIDATION PROGRAM FOR NEW AND ABBREVIATED NEW DRUG APPLICATIONS,@

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ABSTRACT:
This article describes the U.S. Food and Drug Administration (FDA) methods validation program for proposed regulatory methods submitted through the New and Abbreviated New Drug Application processes. The program is conducted by the Center for Drug Evaluation and Research (CDER) and the Office of Regulatory Affairs to ensure that scientifically well-founded regulatory methods are available to assess the quality of the CDER-approved products.[1] The industry, FDA, and United States Pharmacopeia and National Formulary[2] have the common objective of ensuring that drugs in the U.S. marketplace have consistent standards for drug substances and drug product regardless of the synthesis and manufacturing process. This may be accomplished by assuring that the analytical methods for new drug products are submitted for adoption as public standards soon after approval for marketing. The public standard provides a yard-stick for the named product which allows conscientious practitioners and consumers to determine if a product is as purported and thereby be able to detect spurious and sub-standard products in the marketplace.

INTRODUCTION

Validation of the analytical methods cited in a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) is an important part of the U.S. Food and Drug Administration (FDA) drug review process. This validation effort, which is usually performed in two FDA laboratories, together with the validation performed by an applicant provides up to three independent assessments of an applicant's methods to reliably determine the identity, strength, quality, purity, and potency of an approved new drug product. This article provides an overview of the FDA methods validation program conducted by the Center for Drug Evaluation and Research (CDER) in collaboration with the Office of Regulatory Affairs (ORA) for approved new and generic drugs. This article was developed as part of an effort to improve the efficiency of this program.

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[1] With the repeal of Section 507 of the Food Drug & Cosmetic Act, the antibiotic designations, which distinguished them from other drug products, have been eliminated. Methods validation approaches and issues for antibiotic drug products continue as those for all other new drugs currently approved under 505(b) and 505(j).

[2] The United States Pharmacopeial Convention, 12601 Twinbrook Parkway, Rockville, MD 20852.

OVERVIEW

Development of a new drug during the Investigational New Drug (IND) process involves a complex series of nonclinical and clinical studies using pivotal and other clinical trial dosage forms that provide information about its safety and efficacy. This information along with other relevant information is compiled into an NDA that is submitted for review to CDER staff. If the submitted data support a judgment of acceptable risk relative to effectiveness, the CDER will issue an approval letter that allows the NDA applicant to market the drug in the US in accordance with approved product labeling. This labeling provides instructions for use by the health care practitioner and/or patient.

This drug development process also includes characterization studies to establish specifications based on the clinical trial material or pivotal lot used to generate the safety and efficacy database.[3] These specifications ensure the acceptable quality of the drug substance and drug product throughout its shelf life and through post-approval changes, provided no important change occurs in the components and composition and/or method of manufacture of the approved new drug product. The specifications consist of a set of attributes that include the identity, strength, quality, purity, and potency of the drug substance in the drug product (dosage form) in its packaging; methods of assessment; and acceptance criteria.

The maintenance of acceptable attributes throughout the product shelf life is important to ensure that the safety and effectiveness of an approved new drug product is reliably reproduced in patients. Applicants must provide in an NDA the assessment methods and acceptance criteria for chosen attributes in a specification, or reference must made to the United States Pharmacopeia and National Formulary (USP/NF) tests and acceptance criteria. The application specifications may at some later date be adopted to become compendial standards in the USP/NF. The process is generally the same for submission of information in an ANDA, with the exception that a bioequivalence study is used in place of the nonclinical and clinical studies that establish safety and efficacy for an NDA drug product.

For both NDAs and ANDAs, a mixture of public compendial standards and private tests, together with acceptance criteria, are used in the specifications that control the quality of an approved new

[3] For example see International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance "Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological and Biological Products," U.S. Federal Register, 64, (No. 159), August 18, 1999, pp 44928-44935.

drug product. An application may cite five or more separate methods in the drug substance specification and several additional methods in the drug product specification. For NDA applicants, little information is available initially about a new chemical entity (NCE) in a drug product. These applicants often must develop methods for a particular drug substance or drug product without the benefit of any previous experience. In contrast, ANDA applicants may have access to a large body of published scientific information about analytical development including compendial standards for a drug substance and drug product that can be used to support an application. In addition, the generic manufacturer can request through Freedom of Information Act (FOIA) the innovator's analytical methods and tests for the product.

THE CDER AND ORA METHODS VALIDATION PROGAM

Prior to 1962, NDA methods were reviewed to assess their adequacy but were not submitted for laboratory validation. Because many methods subsequently were found not to be suitable for regulatory use, the FDA initiated a laboratory methods validation program as part of the NDA approval process.[4] This program provided independent laboratory validation at two FDA sites to determine the suitability of submitted methods for regulatory purposes prior to NDA approval. The ORA laboratories or the CDER Division of Testing and Applied Analytical Development (DTAAD, St. Louis, MO and Laurel, MD) perform these validations. The ORA NDA drug methods validations are currently assigned from among six Field laboratories including the Philadelphia District Laboratory, San Juan District Laboratory, Winchester Engineering and Analytical Center (Winchester, MA), Northeast Regional Laboratory (New York), Southeast Regional Laboratory (Atlanta), and Pacific Regional Laboratory-Northwest (Seattle). The methods validation program implemented in the seven FDA laboratories helps to ensure the scientific ruggedness and reproducibility of the submitted methods. When both validating laboratories report that the analytical methods are acceptable, the associated reinforcement provides a high degree of certainty that the analytical methods will perform as written.

The FDA's program helps ensure that the quality of all new drugs, and particularly new molecular entities, transfers beyond pre-market approval to routine production. This is accomplished by: 1) requiring the manufacturer to submit method validation information so their integrity and quality can be assessed; 2) documenting that each batch released into the marketplace conforms to the acceptance criteria for tests defined in an approved application or cited in USP/NF compendial standards; and 3) establishing that a competent analyst using the applicant's procedures on agency or commercially available equipment can obtain scientifically valid results comparable to those submitted by the applicant.

In addition, the program provides FDA analysts with experience in the use of specific approaches

[4] Method validations generally are not performed for Over-The-Counter and certain Drug Efficacy Study Implementation-type products (post-1938 to pre-1962 approved products) and, not unexpectedly, inadequate methods are frequent and significant factors in a large number of regulatory actions for these products.

and technologies that are necessary to determine when products are violative and which also may be useful in responding to emergencies. In those instances where the validation shows the methods to give unreliable results, it may be necessary to remove a possibly violative article from the market to ensure the public safety. Methods validation also ensures that methods adequate to support legal and regulatory actions are available and can be used on short notice. These validated analytical procedures are also termed legal reference or referee methods.[5] Validated procedures and USP/NF standards may be used in legal cases to document that an approved drug product fails to meet its quality characteristics. Drugs for which there is a USP/NF compendial are termed *official drugs*, and those without a compendial monograph are termed *unofficial drugs*.[6]

STATUTORY BASIS AND REGULATIONS FOR THE VALIDATION PROGRAM

The adulteration provisions of the Federal Food Drug and Cosmetic Act in Section 501 [351] require that the USP/NF compendial methods be used in determining conformance of official drugs with an *official* standard. If the Secretary of Health and Human Services determines that compendial methods are not suitable to ensure the quality of the product, the publishers are notified of the problem and they are provided an opportunity to promptly establish suitable methods. The Secretary, under certain circumstances to protect the public health, may promulgate regulations establishing appropriate methods and standards if suitable ones are not available in the compendia. Because of this provision in the Act, the new drug regulations permit both NDAs and ANDAs to incorporate, by reference, applicable standards and methods of the USP/NF and to require compliance with current and future revisions of these standards and methods. Although an applicant may use alternate analytical procedures to ensure conformance to the compendial standard, FDA testing to determine whether or not an approved compendial product is violative will be performed in accordance with the standard in the USP/NF.

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[5] T. Layloff and P. Motise; "Selection and Validation of Legal Reference Methods of Analysis for Pharmaceutical Products in the United States," Pharm. Technol., **1992**, 16, 122-132.

[6] Federal Food, Drug and Cosmetic Act, Sec. 201.[321](g)(1): The term "drug" means: (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them.

A compendial standard may be absent in many NDAs and ANDAs. When this occurs, CDER requires submission in the applications of information about the specifications for the drug substance and drug product to ensure identity, strength, quality, purity, and bioavailability.[7] The FDA requirements specify that three copies of the analytical methods and related descriptive information for the drug substance and the drug product contained in the Chemistry, Manufacturing, and Controls (CMC) section be furnished to FDA.[8] After regulatory review, the methods validation portion of the CMC section is sent to the laboratories to perform all necessary tests on the samples and validate the applicant's analytical methods. The related information includes a description of each sample; the proposed drug substance and drug product regulatory specifications; a detailed description of the methods of analysis; supporting data for accuracy, specificity, precision and ruggedness; and complete results of the applicant's tests on each sample. The FDA laboratory staff will generally ask applicants to submit samples directly to the appropriate agency laboratories that will perform all necessary tests on the samples to validate the applicant's analytical methods.

The current good manufacturing practices (cGMP) requirements[9] state that the accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented.[10] This section of the regulations requires a statement of each method used in the testing of the sample including the location of data that establish that the published methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested. The suitability of all testing methods must be verified under actual conditions of use. The FDA's methods validation procedures serve to confirm, in part, compliance with this regulation.

CDER AND ORA GUIDANCES

The CDER and ORA have worked with internal and external constituencies to develop a series of guidances that provide recommendations to sponsors, applicants and review staff on how to characterize a new drug substance and drug product and to ensure its quality attributes over time.[11]

Certain ICH guidance[12] are especially important to the CDER and ORA methods validation programs. These include the ICH Q6A document entitled *Specifications for New Drug Substances and Products: Chemical Substances* and the ICH Q6B document entitled *Specifications for New Drug Substances and Products: Biotechnological Substances*. These documents provide recommendations to sponsors and applicants on how to first characterize a drug substance and

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[7] 21 CFR 314.50(d)(1)

[8] 21 CFR 314.50(e)(2)(i)

[9] 21 CFR 211.165(e)

[10] 21 CFR 211.194(a)(2)

[11] See <www.fda.gov/cder/guidance>

[12] The ICH guidance are also available at <www.fda.gov/cder/guidance>

drug product and then how to set a specification to allow batch release of a drug substance and/or finished dosage form. Both documents encourage reliance, where feasible, on pharmacopeial tests and note the importance of pharmacopeial harmonization. Other ICH guidance documents that support the program include the ICH Q2A document entitled *Text on Validation of Analytical Procedures* and *Validation of Analytical Procedures: Methodology*. The Q2A guidance focuses on:

- the types of analytical procedures under consideration (identification tests, quantitative tests for content of impurities, limit tests for control of impurities, and quantitative tests of the active moiety),
- typical validation characteristics (accuracy, precision, specificity, detection limit, quantitation limit, linearity, range), and
- the need for revalidation under certain circumstances.

The Q2A guidance also defines:

- *repeatability* as the precision under the same operating conditions over a short interval of time, also termed intra-assay precision,
- *intermediate precision* as the variation within a laboratory arising from different days, different analysts, different equipment,
- *reproducibility* as the between laboratories precision based on collaborative studies and usually applied to standardization of methodology, and
- *robustness* as the measure of the capacity of the analytical procedure to remain unaffected by small but deliberate variations in method parameters.

The Q2B guidance further recommends that:

- *repeatability* be determined with a minimum of nine determinations covering the specified range or a minimum of six determinations at 100 percent of the test concentration,
- *intermediate precision* be established by having the tests performed on different days by different analysts using different equipment, and
- *reproducibility* be achieved through an interlaboratory trial leading to standardization of an analytical procedure, such as would be important for regulatory actions.

Procedural guidances have also been prepared to assist sponsors and applicants in meeting the requirements and/or recommendations of the program. An example is the CDER *Guideline for Submitting Samples and Analytical Data for Methods Validation*,[13] which defines *regulatory methodology* as the procedure or set of procedures used by FDA to ascertain whether or not the drug substance or drug product is in conformance with approved regulatory specifications in an NDA. This document notes that compendial methods for articles cited in the USP/NF also may require verification to establish their suitability for that specific drug product. The document defines *regulatory methods validation* as the process whereby submitted analytical procedures are first reviewed for adequacy and completeness and then are tested as deemed necessary in FDA

[13] Available at <www.fda.gov/cder/guidance/ameth.htm>

laboratories. Depending in part on the quality of submitted data, validation may range from step-by-step repetition of an assay procedure to more elaborate studies that include assessment of accuracy, precision, sensitivity, and ruggedness of the method.

Additional guidance for CDER review staff is provided in an October 9, 1996, memorandum from the CDER Chemistry, Manufacturing, and Controls Coordinating Committee's Analytical Methods Technical Committee. This document provides forms and instructions for CDER chemistry review staff to use when requesting methods validation. The memorandum is intended to be used in conjunction with the July 8, 1996, inspection and sample collection guidance cited in the Pre-Approval Inspections and Investigations Compliance Program (CP) 7346.832.[14] This latter document describes procedures for collection and processing samples for different types of analytical work performed by FDA, to include methods validation, profile (forensic), bio-batch, and innovator product sample analyses. Specific procedures to be followed by CDER and ORA personnel performing methods validation are described in Part II, pages 3**B**7 of this document.

VALIDATION OF NDA AND ANDA METHODS

Because certain differences exist in the generation and review of quality information in NDAs and ANDAs, the CDER and ORA methods validation programs for each are described separately.

[14] Available from the CDER FOI Office.

NDA Methods Validation. After evaluation of a methods validation section of an NDA, the review chemist in CDER=s Office of New Drug Chemistry (ONDC) determines which methods should be validated, and submits the package to either Philadelphia, San Juan or DTAAD to perform the validation (CP 7346.832). All Type 1, 2 and 4 NDAs[15] are sent to DTAAD which serves as one of the validating laboratories for these types of validations. All Type 1 through 7 NDAs assigned to the ORA laboratories are sent to the Philadelphia and San Juan District Offices for validation and distribution as needed to either the Northeast Regional Laboratory (New York), Southeast Regional Laboratory (Atlanta) or Pacific Regional Laboratory-Northwest (Seattle). An exception to this general approach is that methods validation requests for radiopharmaceutical products are sent to the ORA=s Winchester Engineering and Analytical Center (Winchester, MA).

After receipt of the methods validation request, the ORA or DTAAD designated validating laboratory notifies the applicant to send the materials required for the methods validation to the validating laboratories.[16] The laboratories then perform the requested methods validation and provide completed reports and worksheets to the ONDC chemist. Summary results are also forwarded to the ORA Division of Field Science and the Compendial Operations Staff in the CDER Office of Pharmaceutical Science. If the methods are found to be unacceptable for regulatory use or, if the two validating laboratories are not in agreement, the reviewing chemist may discuss or negotiate with the applicant to resolve deficiencies or discrepancies. Major revisions to an applicant's analytical methods may require revalidation in the FDA laboratories. If resolution cannot be achieved and a method is not validated, the applicant may invite FDA to their laboratory to observe the performance of the method or be invited to demonstrate the method in a FDA laboratory. In rare instances when the issues are still unresolved, a third party (a laboratory or person(s)) may be selected to act as a referee. The referee(s) findings could result in additional work or information from the applicant or additional analytical data from a FDA laboratory to help resolve the difference(s).

ANDA Methods Validation. ANDA applicants generally have a substantial amount of information on which to base drug substance and drug product analytical development. Published literature and product labeling may provide information about the components and composition of the innovator drug product. Under the Freedom of Information Act (FOIA), NDA product attributes and the methods used to test those attributes may be available but not the acceptance criteria.[17, 18]

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[15] The NDAs are classified: 1. New Molecular Entity (NME); 2. New ester, salt or other non-covalent derivative; 3. New formulation; 4. New combination; 5. New manufacturer; 6. New indication; or 7. Drug already marketed but without an approved NDA. Types 1 and 4 require methods validation for both the new drug substance and the dosage form. Methods for Type 2 require validation only for the active moiety in the drug product but usually are as demanding as other categories.

[16] 21 CFR 314.50(e)(1)(i)

[17] 21 CFR 314.430

[18] 21 CFR 20.61

Optimally there is a suitable official compendial method for the drug substance and/or drug product available that the ANDA applicant may use. This occurs for approximately 65% of ANDA submissions.

For a drug substance, ANDA applicants are not required to use the same synthesis or process as the innovator. A different synthetic process may result in a different impurity profile, acceptance criteria for impurities, crystal form, particle size, and/or residual solvents. Thus the ANDA active drug substance may require a different specification to ensure proper identity and acceptable quality. Similarly for a drug product, generic formulations generally are not required to duplicate those of the innovator.[19] In this circumstance, certain private specifications for a generic product may be required for residual solvents, formulation specific degradants, and different preservatives or antioxidants. A general approach of the ANDA review process is that application specifications in an ANDA may differ from those in an NDA, provided the generic product is pharmaceutically equivalent, bioequivalent and of acceptable quality.

In 1990, the Office of Generic Drugs (OGD) eliminated the requirement of verifying[20] methods for *official* drugs in FDA laboratories, i.e., products where compendial monographs are available for the drug substance and the drug product. Instead the OGD now requires applicants to demonstrate in their submissions that the compendial methods cited in the application are suitable for use for their specific product and thereby could be considered for use in regulatory actions. For the approximately 35% of the ANDA products without compendial methods, OGD review chemists will request that methods validation be performed usually at the ORA district laboratory closest to the ANDA applicant's manufacturing location.[21]

The OGD may waive methods validation for non-compendial products if: 1) the proposed analytical methods have already been validated in an FDA laboratory under another of the same applicant's ANDAs for a similar drug product (e.g., different strength, different packaging configuration), or 2) a monograph exists in the compendium for a similar dosage form (e.g., lyophilized powder vs. ready-to-use solution) and the applicant's proposed regulatory methods are contained therein, providing the change in dosage form will not cause analytical interference in the compendial procedures. Where compendial methods exist, alternate non-compendial methods may be proposed by an applicant and submitted to OGD with suitable validation. However, these

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[19] 21 CFR 314.94(a)(8)(iv)

[20] Verification demonstrates that the method is applicable to the product. This usually is accomplished by analyzing samples prepared by adding known quantities of the drug substance at the dosage levels to the excipient mixture to ensure there is no interference with this determination. Validation requires much more extensive evaluations that are described elsewhere in this article.

[21] In the future OGD review chemists will select an additional FDA laboratory to perform the methods validation so non-compendial ANDA analytical methods will occur in two FDA laboratories, as it does for non-compendial methods cited in an NDA.

alternate methods are not validated in FDA laboratories because the compendial method is the regulatory method. The OGD chemistry reviewers may also ask for additional release and stability tests that are not specified in the USP/NF. Validations for these methods are not requested. On November 25, 1998, the OGD issued a Manual of Policies and Procedures (MaPP)[22] to allow for an approval decision for ANDAs to proceed in the absence of completion of the methods validation similar to the 1981 policy for NDAs.

EXCEPTIONS TO THE GENERAL LABORATORY METHODS VALIDATIONS PROCESS

Depending on the type of submission and the complexity of the methods, validation for some methods may be performed in only one or two FDA laboratories, e.g., cascade impactor particle size measurements for metered dose inhalers. In addition, advances in pharmaceutical and analytical sciences have caused significant increases in the complexity of NDA methods validation packages in recent years. Because of these advances, FDA's laboratories may not have the necessary equipment and/or expertise specified in the application. In some instances, arrangements may be made with an academic institution to assist the FDA analyst in performing the required tests at that site. Because one of the main purposes of methods validation is to ensure that an FDA laboratory is capable of analyzing material for enforcement purposes using the legal reference method, at least one FDA laboratory should be capable of performing methods cited in an approved NDA or ANDA. Maintenance of the requisite expertise and equipment resources over time is difficult, and this type of supplementation with outside academic expertise becomes necessary. In order to minimize this problem, CDER encourages applicants to avoid the use of exotic or unusual equipment to assess attributes when routine technologies will suffice.

The FDA reviewers may require lesser amounts of validation in certain circumstances, e.g., a solution for inhalation or an injection for the same drug substance, or multiple strengths and sizes of the same drug product. However, validation of methods for different strength products may be required because some changes can drastically alter sample-preparation requirements, e.g., tablet or capsule formulations. Other dosage forms also may require unique methods to assess product attributes, e.g., creams and ointments often require extensive sample preparation to extract the active drug substance, micro-emulsion and liposomal products for injection require particle-size testing to ensure stability. Although all products require lot-release testing to ensure consistent product quality, some formulations require more intensive testing to ensure product quality. Examples include modified release products where premature release or the active ingredient could lead to an overdose, aerosol inhalation product particle sizing where particle size growth could effect bioavailability, lipid matrices where coagulation could cause circulatory distress.

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[22] See <www.fda.gov/cder/mapp/5221-1.pdf>

FINALIZING THE METHODS VALIDATION

After analysis, a numerical classification code is given for each methods validation package, as follows:

- *Class 1-- Satisfactory for Regulatory Purposes*. The methods package meets established policy guidelines and is suitable for regulatory purposes.
- *Class 2-- Satisfactory after Minor Modifications.* The methods package is basically satisfactory and suitable for regulatory purposes, except that certain minor modifications need to be made by the firm to make the package correct and complete. Examples could include typographical errors, errors in calculation formulas, ambiguities and omissions, etc., and
- *Class 3-- Unsatisfactory for Regulatory Purposes.* The methods package fails to meet established policy guidelines or is not suitable for regulatory purposes.

Although the final decision rests with the chemistry reviewer, the validating analysts in the ORA or DTAAD laboratories make a determination as to whether the NDA or ANDA method is suitable for regulatory use. If more method development needs to be performed (minor changes- Class 2), then the analysts communicate with the chemistry reviewers as to the deficiencies of the method and the action that they would like the applicant to take. A recent ORA survey conducted on all types of method validations showed that approximately 25% of them failed either at the Class 2 or 3 level. A review of all Type 1 NDA (NMEs) methods validated at DTAAD in 1994 and 1995 showed that only 29% initially met Class 1 standards. The inadequacy of one method validation within the package may constitute a failure of the overall package. Inadequate or absent methods may lead the reviewing chemist to issue a Awithhold approval" recommendation until the problems are rectified.

Post-approval, inadequate methods may lead to the issuance of an untitled or warning letter noting the deficiencies and possible regulatory actions from the inspecting FDA District Office. In addition, issues involving methods have also been a factor in injunctions and seizures. Many regulatory actions relate to lack of or inadequate methods, which are manifested both in inadequate investigations of out-of-specification results and stability data problems. Problems with methods have become more apparent with the addition of experts in analytical chemistry to field inspection teams.

STREAMLINING THE CDER AND ORA METHODS VALIDATION PROCEDURES

The requirement of successful completion of the two FDA laboratory methods validation protocols prior to NDA approval was maintained from the start of the program until 1981 for NDA and 1998 for ANDA applications. In order to avoid delays in the approval process, FDA rescinded this requirement[23] and allowed validation to be completed after approval. The approach assumes that no major problems have been uncovered during the on-going validation work, the methods would

[23] December 4, 1981 memorandum from Deputy Director, Bureau of Drugs. May be obtained from the FDA FOIA Office.

subsequently be satisfactorily validated in FDA laboratories, and any problems encountered in the validation would be resolved. An effort was begun in July 1997 to re-engineer the process and to bring the Agency's methods validation program more in line with other NDA and ANDA streamlining efforts. Based on this effort, certain changes to the program are being effected. Examples include the following:

- Unless specifically requested by OGD and/or ORA investigators, laboratory verification for compendial ANDA products will no longer be performed. The ORA resources, which had been devoted to this effort, will be directed to validation of non-compendial NDA and ANDA methods.
- Methods validation for non-compendial NDAs and ANDAs will consistently be performed in two laboratories and efforts will be made to reduce the timelines so the process is completed prior to the final review decision.
- Compendial tests such as pH measurements, IR spectral comparisons, and water content assessments will no longer be routinely validated.

WHY MAINTAIN A METHODS VALIDATION PROGRAM?

This program is costly because the laboratories used in the program are expensive to equip and maintain. In addition, recruitment and retention of the highly skilled analytical chemists needed for its successful implementation are also difficult. Despite these costs, FDA's program is a highly effective and efficient way to help ensure the quality of new drug products available to the US health care practitioner and patient. Arguments in support of maintaining a strong methods validation program are considered in the following sections of this report.

Science-Based Specifications

The FDA methods validation program approximates an intermediate level of validation similar to those utilized by Environmental Protection Agency and AOAC International. An even more elaborate type of methods validation is used by these and other organizations under certain circumstances. These more elaborate approaches are not considered needed in FDA's program because of:

- the wide acceptance criteria compared with repeatability and/or reproducibility coefficients of variations in the methods;
- the small differences in the amount of the analyte; and
- the use of well-defined, non-interfering matrices.

When a private specification is submitted through the USP/NF adoption process there is additional protection to ensure that a method is suitable for its intended use because the process promotes public review and comment. Also, USP/NF requires that official drugs have no added substances present that could interfere with the official methods of analysis. Further, individual manufacturers must ensure that the individual components and/or the aggregate of components in the drug product do not bias the analytical results. As the concentration of the analytes decrease and their number

increases, product matrices become more complex (e.g., botanicals, natural extracts), and acceptance criteria for low-concentration inactive substances and impurities decrease there will be additional challenges to the approaches employed by the FDA and USP/NF to develop compendial standards.

The NDA and ANDA applicants provide repeatability and intermediate precision determinations (within laboratory variances) while others, including the FDA through its validation process, provide an estimate of the method reproducibility (among-laboratory variance). Although repeatability and intermediate precision are useful to assess performance of a method initially, reproducibility and ruggedness are the important regulatory parameters since products generally are tested in different laboratories to determine compliance with the standards.

Transition of Quality Control and Quality Assurance to the Applicant

Over the past 20 years, the focus of FDA laboratories to ensure the quality of approved drugs in the US marketplace has shifted away from surveillance. In the 1970s CDER's laboratory staff commitments to surveillance were over 100 Full-Time-Equivalents (100% of the National Center for Drug Analysis, 20% of the National Center for Antibiotic Analysis, 20% of the Division of Drug Biology and 15% of the Division of Drug Chemistry).[24] In place of these units, FDA has focused on a 'first-party' approach to ensure the quality of CDER-approved drug products in the US marketplace. The extensive methods validation program coupled with an intensive Agency review process of detailed application commitments requires the NDA and ANDA applicants to maintain strong quality assurance and quality control programs. The general approach has been highly successful and has reduced the need for intensive post-marketing surveillance testing. The limited high risk targeted surveillance testing which currently is performed demonstrates that the quality of pharmaceutical products regulated by CDER in the U.S. marketplace is remarkably high. Furthermore, the cGMP requirements, and rigorous compliance and field inspectional activities help ensure that out-of-compliance products will be removed from the marketplace. A recent estimate is that the costs of all the quality testing that the FDA performs each year, both for methods validation and for inspectional activities, is approximately $60 million. This is an extremely small investment to ensure the quality of marketed goods that yield up to $100 billion in sales per year.

Violative Articles and Regulatory Action

The CDER/ORA drug regulatory system has stringent tools available that may be used to enforce compliance with requirements, e.g., recalls, seizures, injunctions, and prosecutions. The CDER and ORA methods validation program provides a critical component in FDA's enforcement activities by assuring that the tests and methods in an NDA and ANDA, or in the USP/NF, may be

[24] The ORA Field laboratory personnel commitment probably exceeded this number.

used as a basis for determining that an applicant's drug substance and/or drug product are violative. With the reduction of post-approval product collection and analysis surveillance activities, up-front validation of methods becomes more important to ensure that firms are in compliance with the applicable regulations. The independent validation in two FDA laboratories is needed not only scientifically but also because the two FDA laboratories frequently uncover different problems with a firm's analytical methods.

Development of Public Standards

The FDA's methods validation program should be an integral part of an industry, FDA and USP/NF collaborative effort to facilitate the transition from private specifications to public standards in USP/NF monographs.[25] The availability of these validated methods, as published USP/NF monographs, would enable the FDA to have ready access to the legal reference methods throughout the Agency without having to go to the firm or document storage rooms to obtain them. In addition, the USP/NF monograph revision process is subject to public scrutiny that adds to the credibility of the published methods. The establishment of public standards in the USP/NF could be initiated by the manufacturer submitting to the Committee of Revision (COR) of the USP/NF these approved specifications in a monograph form with the recommendation that they be adopted as public standards. The manufacturer could also request that the FDA release the pertinent methods validation assessments to the COR. Although additional testing may occur at the time an analytical method is published in the Pharmacopeial Forum (PF), an official notice and comment publication of the USP/NF, the validation that FDA performs in two laboratories provides the primary independent assessment of a firm's analytical methods. The COR could then review and comment on the material before publishing the proposed monograph for adoption consideration in the PF. With the publication of a draft monograph in the PF, other interested parties are expected to assess the applicability of a proposed standard and methods to their own products and to submit comments as appropriate via the PF process. Following review of all submitted information, and perhaps following requests for further information and testing, the COR may adopt the monograph that includes the standard with the test methods and acceptance criteria. After the COR adoption, the monograph becomes official in the USP/NF.

FUTURE CHALLENGES

The development of analytical methods to ensure the quality specifications of a product approved through the NDA or ANDA processes and the subsequent validation by the FDA laboratories creates a private quality standard, i.e., an agreement between the applicant and FDA on product specifications. This information and the results of the methods validation are not available to the public. In an effort to effect a transition of private specifications in an NDA or ANDA to public information, FOIA rulings at the Agency in the mid-1970s allowed that methods of analysis could be made public after an NDA and ANDA was approved. Agency interpretations of the application

[25] 21 U.S.C. 377 states "The Secretary, in carrying out the provisions of this chapter, is authorized hereafter to cooperate with associations and scientific societies in the revision of the United States Pharmacopeia."

of FOIA in CDER have concluded that the attribute and analytical procedure of a specification may be shared but not its acceptance criteria. Through the validation and approval process, the drug substance supplied by the applicant is the de facto reference standard.[26] Just as the methods are not publicly available, reference standards for these products frequently are also not available.

The establishment of private standards and the unavailability of appropriate reference standard materials fail a primary need of public commerce in a free market (i.e., to be able to independently determine if a product meets its purported quality standards). In order to properly address this issue, the industry and FDA, working with USP, as appropriate, should establish an efficient, timely, and cost-effective transition from private to public standards. The FDA should also work with applicants, USP, international groups, and other organizations, as appropriate, to consider further ways to validate analytical methods for private specifications and to assist in the transition of these private specifications into public standards. Although FOIA rulings at the agency have limited the public availability of information about the acceptance criteria for an analytical method, such information may be made available in the future.[27] The availability of public standards facilitates international commerce and provides to conscientious practitioners, consumers, and regulators the opportunity for independent product quality assessment. This empowerment of the public to independently assess the quality of marketed products should significantly stem the trafficking and reduce the market share of spurious and substandard products not only in the U.S. but also in the world's marketplaces. To further this empowerment, the public standards should in some monograph aspects include quality assessment technologies and tools that are inexpensive, readily available and cost efficient. The reduction in the trafficking of spurious and substandard products will help level the market playing field, which will assist the ability of conscientious manufacturers to compete in the marketplace. In addition, this market place cleansing will make great strides in assuring that the marketed products are indeed safe and effective.

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[26] In the case of antibiotics the submitted drug substance was formerly designated as the "Master Standard" for that product.

[27] 21 CFR 314.430 (e)(6) cites "After FDA sends an approval letter to the applicant, the following data and information … are immediately available for public disclosure … An assay method …"

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