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Drug Approval Process and Regulatory Requirements

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1.1 Introduction

The role of the Food and Drugs Administration (FDA) in the review and approval of pharmaceutical products is divided into two broad categories. Each of the categories has its own set of regulations and issues, but regardless, they are designed to protect patients against harm and ensure the effectiveness of the medical products. These medical products include drugs from animals, plants, or human origin and products obtained via synthetic pathways, medical devices, and combination products.

The two categories are as follows:

1) Analytics in the discovery process (R&D) of pharmaceutical products
2) Analytics in the compliance of products to their standards in the marketplace

Broadly speaking, the first category is a proactive approach while the second category is reactive. The first category ensures the safety and effectiveness of the products via the requirements for new drug applications (NDAs) and biologic license application (BLA) and occurs in the R&D phase of development of products, while the second category ensures that the manufacture of these products follows the NDA/BLA when they reach patients. The quality, safety, and effectiveness of pharmaceutical products are indicated via analysis of products that act as surrogates for these characteristics.

The nature of pharmaceutical products is their uniqueness that creates problems, issues, as well as challenges. A validated analytical procedure that works for one product might not provide for validation of the method for other products. The concept of validation must be applied in a flexible way to allow for changes due to the nature of a product, its chemical pathway, its origin and the nature of the APIs and inert ingredients (excipients) used for its manufacture. These issues will occur in both categories, and attempts to provide guidelines should include a more flexible approach that is not used presently.
The increase in regulatory requirements, often as a reaction to some perceived, potential, or real problems has increased the cost of development and compliance of pharmaceutical products. This is compounded by an adversary relationship among the regulatory agencies and pharmaceutical/biotech industry. In a perfect world, they should work in tandem in a win–win approach on scientific requirements and methodologies since they both have the same purpose, to ensure safety and effectiveness of pharmaceutical products.

However, before reviewing the role of FDA in the analytic areas, it would be of interest to briefly describe the FDA role by which a new drug entity is developed and approved.

In this chapter, we review in more detail the role of analytics required by FDA to approved products, to approve changes in products and to ensure through compliance that manufacture done according to NDAs will yield a quality product that is safe and effective. However, it is also important to discuss in some detail the good laboratory practices (GLPs) in 21CFR 58.

1.2 The Regulatory Process for New Drug Entity

A simplified schematic description of the overall FDA process [1] is shown in Figure 1.1.

1.2.1 Preclinical Studies

The organization will perform animal- or cell-based tests to determine if the drug is preliminarily safe and could become a candidate for human clinical trial. General guidance for these studies is provided by FDA, but must be adapted to the nature of the tested product. This is followed by one or more meetings with FDA, which reviews the data and, if necessary, requests additional data or clarifications. You can obtain guidances through the FDA website or through the Government Printing Office website.

1.2.2 Investigational New Drug Application (INDA)

The next step is to complete an INDA (21 CFR 312). Various “guidance for industry,” some based on ICH, are available from the FDA website. Following review by FDA of the INDA and approval, clinical trials are conducted in Phase 1, Phase 2, and Phase 3.

1.2.2.1 Phase 1 Clinical

Initial introduction of the investigational drug to 20–30 patients or normal volunteers to determine safety, pharmacologic actions, side effects associated with increased doses, and mechanism of action.
1.2.2.2 Phase 2 Clinical
Controlled clinical study to evaluate effectiveness and risks using hundreds of patients.

1.2.2.3 Phase 3 Clinical
Expanded trials to show effectiveness in several thousand patients.

1.2.3 New Drug Application (NDA)

1.2.3.1 NDA Review by FDA
For NDA with a high urgent priority, the review of the application will take about 6 months on average. For other NDAs, the target is to complete the review in 22 months.

Figure 1.1 Schematic high-level representation of the overall FDA review process [1].
1.2.3.2 NDA Review Process
See in Figure 1.2, a generalized NDA review process that was adapted by Dabbah [1] based on Mathieu [2].

**Figure 1.2** Generalized NDA review process from Dabbah [1], which was adapted from Mathieu [2].
1.3 Good Laboratory Practice for Nonclinical Laboratory Studies

The intent of this section is not to reproduce the 21CFR-58 that one can obtain easily through the Internet, on the FDA website. The intent is to extract items
that relate directly or indirectly to the analysis of pharmaceutical products, that would be applicable to products in development as well as to products that are on the marketplace. The scope of the regulation is large, but we will confine our discussion to human and animal drugs, medical devices for human use, and biological products. We will not discuss the animal facilities or the electronic products used [3].

The term of analytics applies to analysis of products using methods and procedures that have been validated for each of the products in question, and these tests are conducted according to protocols also called standard operating procedure (SOP) that would allow a consistent analysis of products. The results of analysis should ensure that the quality of the products fulfills the requirements of the NDAs for these products. If a test procedure has been validated, but the application of the test to the products is not done under a strict protocol, the credibility of the results will be in question, and the release of products to the marketplace will be harmful to patients and will also be illegal. The SOPs will include the environment of the laboratory where testing is being done. It goes without saying that an analysis must be performed by trained and skilled personnel under the supervision of the testing facility management or its delegate.

A requirement of GLPs is that there is a Quality Assurance Unit in the organization that will approve developed protocols designed to ensure the credibility of the results of analysis. Deviations in protocols must be approved by the Quality Assurance Unit before they are implemented.

Perhaps, one of the most important factors in assessing the credibility of analysis is the calibration of equipment for the purpose intended [4]. A credible analysis starts with the choice of a test article that should be representative of the tested system or the production batch. For example, in microbiological testing, microorganisms are not homogeneously distributed, thus representative sampling is a must. The use of control articles or reference standards is indicated in protocols to ensure that the tested article has the appropriate quality, strength, identity, purity, and composition to ensure the efficacy of the products.

The reporting of results of analysis must be based on the actual analysis of a product that is documented, archived, and retrievable.

1.4 Validation of Analytical Procedures: Methodology

Every analytical procedure must be validated. Guidance and recommendation are shown in Guidance for Industry: Q2B Validation of Analytical Procedures: Methodology, which was developed by the International Congress on Harmonization (ICH) and adopted by FDA in November 1996 [5]. Since these are guidelines, other approaches to validation may be acceptable.
The main objective of validation of an analytical procedure is to demonstrate that the test is suitable for its intended purpose. In general, one wants to determine the capability of the procedure in terms of specificity, linearity, range, accuracy, precision, detection, and quantitation limits. In Chapter 5, there is an extensive discussion of these characteristics applicable to most analytical procedures but might require some modifications due to the nature of the procedure and its applicability.

In the Guidelines for Industry on Validation of Analytical Procedures [6] (ICH-Q2A, which was also adopted by FDA (March 1995)), there is a general discussion of the seven characteristics shown earlier. It also adds a section on the revalidation of the validation of analytical procedures. It should occur when there are changes in the synthesis of the drug substance, changes in the composition of the finished product, and changes in the analytical procedure.

The US Pharmacopeia information on the validation of analytical procedures should be consulted, inasmuch as that they are cited and applicable for products that are approved by FDA. These US Pharmacopeia (USP) chapters are <1223> Validation of Alternative Microbiological Methods [7]; <1225> Validation of Compendial Procedures [8]; <1227> Validation of Microbial Recovery from Pharmacopeial Articles [9] and <85> Bacterial Endotoxins Test [10].

1.5 FDA Role in the Discovery and Development of New Drug Entities

Each new drug, device, or biological is unique; thus, a single regulatory process that ensures safety and effectiveness is not desirable. Thus, the manufacturer of new entities must provide data on analytical procedures that include validation of analytical methods as well as adherence to GLPs as indicted earlier. If the FDA reviewer is not satisfied with the analytical data presented or the interpretations of these results, he/she might require additional data. It is a fact of practice that the manufacturer will not present all analytical data available, but only those that are required as a minimum. The approval process will go faster if manufacturers would provide to FDA all data that are available, even negative data. Small organizations as well as start-up organization that do not have too much experience dealing with FDA will tend to use the guidelines for industry to the verbatim, even when the nature of the new products is such that it does not require following these guidelines to the verbatim.

1.5.1 INDA Analytical Requirements

In this section, we look at the requirements for the development of analytical data. Before a drug entity is to be used for clinical trial, that is, administered to
humans, the process includes an investigational new drug application (INDA). The INDA gives a general idea of pharmacological effectiveness and safety. The tests performed include screening via in vitro methodologies; pharmacodynamic testing via qualitative and quantitative pharmaceutical profile such as dose response, mechanisms of action, and interaction with other drugs; pharmacokinetics through bioavailability, accumulation, and clearance of the product and species to species differences. The assurance of safety is much more complicated and includes toxicological testing, via acute toxicity, subacute and chronic toxicity, carcinogenicity, reproductive toxicity, genotoxicity, and toxicokinetics testing. Each of the areas listed will yield credible and useful data if the procedures used are completely validated and follow the requirement of GLPs. Of more direct interest in this section in the INDA is the section on chemistry, manufacturing, and control (CMC). The chemical, physical, and biological characteristics of the drug are provided along with the validated analytical procedures that will be used to determine the identity, purity, potency, and quality of the drug substance [11]. The information that is required depends on the phase of the investigation, risks, novelty of the drug, previous studies, route of administration, and the patient population targeted. At the INDA level, especially in Phase 1, there is a requirement for brief description of analytical procedures to be used. In the subsequent phases, there should be a list of tests performed, such as for the identification of impurities that should be qualified and quantified. If USP analytical procedures are used, they should be described in general terms. However, if non-USP analytical procedures are used, there is a need for a complete description including validation data [11]. The clinical investigation can start 30 days after the FDA receives the INDA application, unless FDA decides not to allow the start of the clinical phase. The reason for a hold on clinical investigation can be that FDA needs additional technical data, such as appropriate validation of the analytical procedures to be used or perhaps that the risk to patients is too high.

1.5.2 NDA Analytical Requirements

NDA requirements are covered in detail under 21 CFR Part 314. From an analytical point of view, there should be a description of analytical methods, their rationale for use, and appropriate statistical analysis. The CMC section includes references to the USP analytical methods as well as to non-USP analytical procedures with appropriate validation data. It is understood that both for INDA and NDA data presented to FDA have been obtained under GLP guidelines.

1.5.3 Biotechnology-Derived Products – Small Molecules

In 1999, ICH developed a Q6B guidance that was adopted by FDA as guidance for industry. It is titled Q6B Specifications: Test Procedures and Acceptance
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Criteria for Biotechnological/Biological Products [12]. The objective was to provide guidance on general principles for the setting and justification of a uniform set of specifications for these products. Specifications, according to the guidance, are defined as a list of tests, reference to analytical procedures, and acceptance criteria. Conformance to specifications means that, when tested, using the analytical procedures indicated, these products will meet the acceptance criteria.

The analytical methods for biotechnology-derived products are very complex and mainly apply to large molecules. On the other hand, biotechnological processes can also lead to the development of small molecules, which will follow the requirements of drugs modified by the nature of the process and its process- or product-related impurities.

1.6 FDA Inspectors’ Role in Analytics Relative to Products in the Marketplace

Drug manufacturing inspections are part of the overall involvement of FDA in ensuring the effectiveness and safety of products on the marketplace. The FDA has issued a number of guidance documents in its compliance program. We will review the general guidance for compliance, the guides for inspection of quality control laboratories, the biotechnology inspection guide, and the guide for inspection of microbiological quality control labs as they related to test procedures used, which constitute the overall area of analytics. The comprehensive regulatory coverage of all aspects of production and distribution of drugs that meet the requirements of the 501(a)(2)(B) becomes consistent across the pharmaceutical industry, thus reducing variations in compliance inspections.

1.6.1 FDA Compliance Program Guidance Manual (Implemented on 09/11/2015 with a Completion Date of 09/11/2016 – Program 7356.002)

The guidance manual [13] evaluates through manufacturer’s inspections such as the collection and analysis of samples, the conditions and practices under which drugs and drug products are manufactured, packed, tested, and stored. Inspections are conducted every 2 years and zero in on compliance to current good manufacturing practices (cGMP)s. In this section, we deal with laboratory control systems. These include the availability of approved procedures and their documentations. The laboratory can have written approved procedures, but the role of the FDA inspector is to determine if the written procedures are used in the performance of analytical procedures. As the inspection proceeds, results might require a more in-depth investigation. For example, are the personnel qualified and trained to accomplish the various analytical procedures?
the equipment available adequate and calibrated? If computerized or automated systems are used in connection with the analytical tests, are these systems validated? Are reference standards used in the analysis or are the standards used equivalent to the official reference standards? Are the required tests performed on the correct samples? Are all the records of the performed testing available? What is the out-of-specification (OOS) procedure and is it followed? Of major interest to FDA is the issue of the adequacy of samples used for analytical testing [14].

The FDA inspectors, often, are faced by the following issues in the laboratory control system that need to be remedied:

a) Pattern of failure to establish and follow a control system for implementing changes in laboratory operations  
b) Pattern of failure to document investigation of discrepancies  
c) Lack of validation of computerized and/or automated processes  
d) Pattern of inadequate sampling practices  
e) Lack of validated analytical methods  
f) Pattern of failure to follow approved analytical procedures  
g) Pattern of failure to follow an adequate OOS procedure  
h) Pattern of failure to retain raw data.

1.6.2 Guide for Inspection of Microbiological Pharmaceutical Quality Control Laboratories

This is a specialized field of analysis that is often a reason for recall of products due to potential nonsterility or the presence of microorganisms that can be dangerous to the public at large and especially to immune-compromised patients. This guide addresses many of the issues associated with the chemical aspects of laboratory analysis of pharmaceuticals, but we would be remiss not to examine it in detail [15].

a) For pharmaceutical products that are nonsterile, the total microbial count would be an indicator of contamination if they exceed a certain limit. USP, in its monographs, addresses this issue by including microbial counts in the monographs. It also includes, when appropriate, the absence of certain specified microorganisms. These were determined by taking into consideration the use of the product, the nature of the product, the route of administration, and the potential hazard to the user. An FDA inspector should carefully review the microbiological testing of topical drug products, nasal solutions, and inhalation products, which appear to have a number of microbiological problems [16]. USP provides analytical methods for specified microorganisms [17], but it is the responsibility of the manufacturer to determine the native microbial population and, based on a risk/benefit analysis, to test for other microorganisms using a validated microbiological
method. The advent of automated microbiological systems for count and speciation of microorganisms requires that the analytical method used is equivalent or better than the USP procedure. Faced by this issue, an FDA inspector will request comparative data between the USP method and the method used by the manufacturer’s laboratory.

b) A number of products contain preservative, especially products used as multidoses. The procedure used should include neutralizing agents; otherwise, the results of microbiological testing will not be valid. In terms of validation, the USP procedures are validated, by definition. However, each drug substance or finished product contains inert ingredients that might interfere with the microbial tests. It will be necessary for the FDA inspector to request data on the validation of a microbiological analysis for a particular drug substance or finished product.

c) Media are necessary in most microbial tests, and the process used for preparation and use of media must follow an SOP. For example, sterilization of a medium must be validated. The environment of a microbiological testing laboratory is critical and needs to be monitored and controlled to ensure credibility of the microbiological testing results. Cross-contamination of samples must be avoided or at least minimized.

d) Sterility testing [18] has been an issue in recall of product for potential non-sterility. The test itself is subjected to contamination, unless precautions are taken to avoid contamination of samples. Robotic systems have been used, but might introduce a false sense of security. Similarly to any other system, the robotic instruments operation should be validated.

e) Procedures for microbial testing of product might originate in the USP, bacteriological analysis manual (BAM), or other microbiological references. The FDA inspector will evaluate the methodologies used and make sure that the laboratory has the equipment and instruments to conduct the test available and calibrated.

1.6.3 Biotechnology Inspection Guide

This is a specialized area that requires an understanding of the science and its application to the manufacture of biotechnology-derived products. The same basic regulations and requirements are applicable to these biotechnology-derived products if they are as small molecules. The FDA inspector should review the following areas to determine if deficiencies exist [19]:

a) The training of the laboratory personnel should be adequate for the performance of specific and complicated analytical procedures.

b) Equipment maintenance/calibration and monitoring should be documented, and a maintenance schedule should be available. All analytical methods should be validated with the equipment and reagents specified in the analytical procedures.
c) Reference standards or reference materials should be well characterized, properly stored, and utilized during testing.

d) Laboratory operating procedures should be available and followed.

1.7 Conclusions

- Analytical procedures are central to the assurance of the safety and effectiveness of drug substances, drug product, and biotechnology-derived products as well as biological product.
- Development of data must be done under GLPs to be incorporated in requests for marketing approval.
- Validation of analytical procedures ensures that the purposes of analytical procedures are fulfilled and is credible, thus protecting the patients and the consistency of manufacturing batches.
- Laboratories that perform analytical procedures must fulfill strict requirements in terms of their environments, the documentation of testing, the training of analysts and their skill levels, commensurate with the complexity of the analytical procedure used.
- The suitability of an analytical method for testing a given product must be established.
- Changes in analytical procedures should be justified and, when significant, must be approved by FDA under an amendment to the NDA. Revalidation of analytical methods should be done routinely at specified intervals or when changes in manufacturing process and/or ingredients are introduced.

The publication of guidance by FDA to its inspectors in evaluating the analytical procedures and for conformance to the approved marketing orders gives to the manufacturers a heads-up on what to expect during FDA inspections. Actually, these manuals should be used by manufacturers in preplanning for actual FDA inspections.

References

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