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New Drug Application

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ABSTRACT
During 2019, the FDA received 618 investigational new drug (IND) applications and approved 48 NDAs.1 IND applications consist of preclinical data, human subject experimentation design, and other components that require analysis and approval by the FDA before Phase I testing. NDAs consist of all the information in an IND plus phase I–III clinical trial data and are required for drug approval. The approval process is complex, and the NDA is the last major hurdle to overcome before the drug enters the market. Throughout this chapter, we will discuss the importance of the NDA and provide a foundation as well as resources on this vital step in drug approval.This chapter delves into the concept of drug repurposing, which involves identifying new therapeutic applications for existing drugs. Drug repurposing offers a cost-effective and time-efficient approach to drug discovery by leveraging the knowledge and safety profiles of approved or investigational drugs. The chapter provides an overview of the principles and strategies employed in drug repurposing, including high-throughput screening, repurposing based on mechanistic insights, computational methods, and the increasing role of artificial intelligence in drug repurposing, as this is an emerging trend in the field. It explores successful case studies where repurposed drugs have shown promise in treating different diseases. Furthermore, the chapter discusses the challenges and opportunities associated with drug repurposing, including regulatory considerations and intellectual property issues. Overall, this chapter serves as a valuable resource for researchers and professionals in the field of drug development, emphasizing the potential of repurposing existing drugs to address unmet medical needs.

I. INTRODUCTION

The submission of a new drug application (NDA) to the Food and Drug Administration (FDA) is an official request by a pharmaceutical company (applicant) to sell and market a drug in the United States. When complete, an NDA will contain thousands of pages of nonclinical, clinical, and drug chemistry information that supports the proposed labeling of the product.

Pharmaceutical companies take years developing the content of the NDA during the investigational new drug (IND) stage of the drug development process. Although the content of an NDA is defined by regulation, each NDA will be unique due to the disease or condition being treated and the characteristics of the investigational drug. Since each application will be it is critical for a pharmaceutical company to obtain guidance from the FDA at each phase of drug development. This will ensure that the proper efficacy and safety data are developed to support the filing of the NDA. The presentation of the efficacy and safety information in the NDA is critical to a successful review and subsequent approval of the application. the applicant should ensure that the information is presented clearly and consistently throughout the NDA. The submission should be organized following the format of the Common Technical Document (CTD) and published electronically to facilitate review by the FDA.[1]

The electronic format also facilitates the submission of the NDA through the Electronic Submission Gateway at the FDA. Once the NDA is submitted, the application will move through the review and approval process. Over the course of 8-12 months, specialized review teams at the FDA will evaluate the different technical sections of the NDA to see if the data support the proposed product label. In addition, representatives from the FDA will conduct audits of the applicant, clinical study sites, and drug manufacturing facilities to ensure the integrity of the information in the application. During this time, the applicant will work closely with the FDA review team to respond to questions, facilitate the audits, and negotiate final labeling for the drug. While the statute governing the NDA process requires that the article be "safe for use" and "effective for use," it does not define these terms. The US Supreme Court interpreted these requirements as follows: A drug is effective if there is general recognition among

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experts, founded on substantial evidence, that the drug in fact produces the results claimed for it under prescribed conditions. Effectiveness does not necessarily denote capacity to cure. In the treatment of any illness, terminal or otherwise, a drug is effective if it fulfills, by objective indices, its sponsor's claims of prolonged life, improved physical condition, or reduced pain... Few if any drugs are completely safe in the sense that they may be taken by all persons in all circumstances without risk. Thus, [the FDA] generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use. The FDA has not only adopted this interpretation but has also developed content requirements for an NDA that implement these principles. The required content of an NDA is outlined in the Food, Drug, and Cosmetic Act (FD&C Act) and Title 21 of the US Code of Federal Regulations (CFR). Applicants should follow these requirements to assure that their NDA provides enough information to enable the FDA reviewers to reach the following key decisions: Whether the drug is safe and effective in its proposed use(s) and whether the benefits of the drug outweigh the risks. Whether the drug's proposed labeling (package insert) is appropriate and what it should contain Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity. Based upon the outcomes of their review, the teams will make a final approval If approved, the applicant may market the drug according to its approved labeling and initiate post approval monitoring of the drug to maintain the NDA. This chapter will provide an overview of an NDA by presenting the regulatory requirements, the development and presentation of the content, the review and process, and the required maintenance of the NDA.[2]

LAWS, REGULATIONS AND GUIDANCES

The Federal FD&C Act is a federal law (statute), enacted by Congress, granting the FDA the authority oversee the safety and efficacy of drugs in the United States. Section 505 of the FD&C Act [21 United States Code (USC) 355] clearly establishes the requirement for and approval of an NDA prior to an applicant marketing a new drug in the United States. The law states that "No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application is effective with respect to such drug. A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling proposed to be used for such drug; and (G) any assessments required under section505B. The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. In order to ensure that the requirements of the FD & C Act are met, the FDA issues regulations. [3]

There are many regulations that are pertinent to this chapter; however, the regulations defining a "new drug" and the requirements regarding applications to market a new drug are critical to understanding this chapter. The regulations in 21 CFR Part 310 titled "New Drugs" outline the scope of a new drug as any changes to a molecular entity, no matter how small, which have not been the of an approved NDA or "grandfathered" (those drugs sold prior to 1938). Consequently, articles that are "new" and not marketable without further testing include a new substance, even a coating, excipient, or carrier of the drug; a new combination, even of individually approved drugs or if the proportion of ingredients in the combination has changed; a new use; or a new dosage, duration, or method of administration." The purpose of the regulations, as outlined in Part 314.2, is to establish an efficient and thorough drug review process to (1) facilitate the approval of drugs shown to be safe and effective and (2) ensure the disapproval of drugs not shown to be safe and effective. These regulations are also intended to establish an effective system for FDA's surveillance of marketed drugs.

These regulations shall be construed in light of these objectives. Of particular relevance to this chapter are the regulations in 21 CFR Part 314.50, which outline the primary content and format of the NDA. The required content will be discussed in greater detail later in this chapter and

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presented in the format of the CTD. In addition to the regulations, numerous guidance documents have been established by the FDA that represents the current thinking of the Agency on the content and format of an NDA. Guidance documents can be best accessed through the FDA Website, http://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The FDA publishes these documents to provide applicants with guidance on how to be compliant with the regulations. Guidance documents are not considered law; therefore, they are not legally binding on the public or the FDA. Thus, applicants may use alternative approaches to satisfy the applicable statutes and regulations. The FDA has published a series of guidance documents regarding the format and submission of an NDA using the electronic CTD (eCTD) format. Certain guidances, such as "Guidance for Industry Providing Regulatory Submissions in Electronic Format-Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications," provide general guidance on how to organize information in the application while others, such as"M4: Organization of the CTD, M4Q: The CTD-Quality; M4S- The CTD Safety; and M4E: The provide guidance on the information to be included in the technical sections of the application. When preparing for the submission of an NDA, applicants should be aware of ongoing changes to laws, regulations, and guidances as they may impact their NDA submission. In 2012, The FDA Safety and Innovation Act (FDASIA) was passed. [4]

This law included the of the Prescription Drug User Fee Act (PDUFA) which authorizes the FDA to collect fees from companies that produce certain human drug and biological products. The fees ensure that the FDA has the necessary resources to maintain a predictable and efficient review process to expedite the drug approval process. PDUFA must be reauthorized every five years. The government has established multiple performance goals with the reauthorization of PDUFAV through the year 2017 which will impact the submission of an NDA. To begin with, an. applicant will continue to pay user fees to file an NDA and begin the review process. For full NDA applications requiring review of clinical data, the fee is US$1,958,800. If the application does not require review of clinical data or is a supplemental application requiring review of clinical data, the fee is US$979,400. These amounts became effective on October 1, 2012, and are updated annually."

There are no fees payable if the FDA refuses to file the NDA.12 Given the complexity of the applications and the need for additional time to meet with applicants, PDUFA V also increases the time allowed for the Agency to complete its review of the application. Priority applications being reviewed under the V program will now be reviewed in eight months instead of six months, and standard applications will be reviewed in 12 months instead of 10 months. As can be seen, an applicant needs to be aware of changes to laws, regulations, and guidances when preparing an NDA. Revised user fees, revised review processes, and timelines and electronic submission requirements are all examples of changes that can affect the submission of an NDA. In addition to knowing the laws and regulations that outline the requirements of an NDA submission, applicants should be aware of the laws and regulations that provide exceptions to those listed above. The Orphan Drug Act (see Chapter 7) allows the FDA to grant special status to a drug intended to treat a rare disease or condition. To qualify for Orphan status, the drug must be intended to treat a disease or condition that affects fewer than 200,000 people in the United States each year. With so few patients, it would be difficult for the applicant to recoup the development cost. Therefore, the Act provides incentives to applicants to develop these drugs. One incentive is a waiver of the PDUFA fee.[5]

DEVELOPMENT OF THE NDA

Pharmaceutical companies take years developing the content of the NDA as part of the drug development process. This process, as shown in Figure, is not only time-consuming but is also costly. The cost of bringing a drug to market has been reported to be over US$1 billion; however, when you factor in the costs associated with drug development failures, the estimated cost in research dollars spent for every drug that is approved soars to US$4 billion. Given the high costs of time and money, an applicant should not wait until the end of its pivotal studies to start thinking about the submission of an NDA. To ensure that the necessary information is available for the NDA, careful planning should begin and continue throughout all stages of development. This can be accomplished by outlining an approval pathway for the new drug in a regulatory development plan (RDP).

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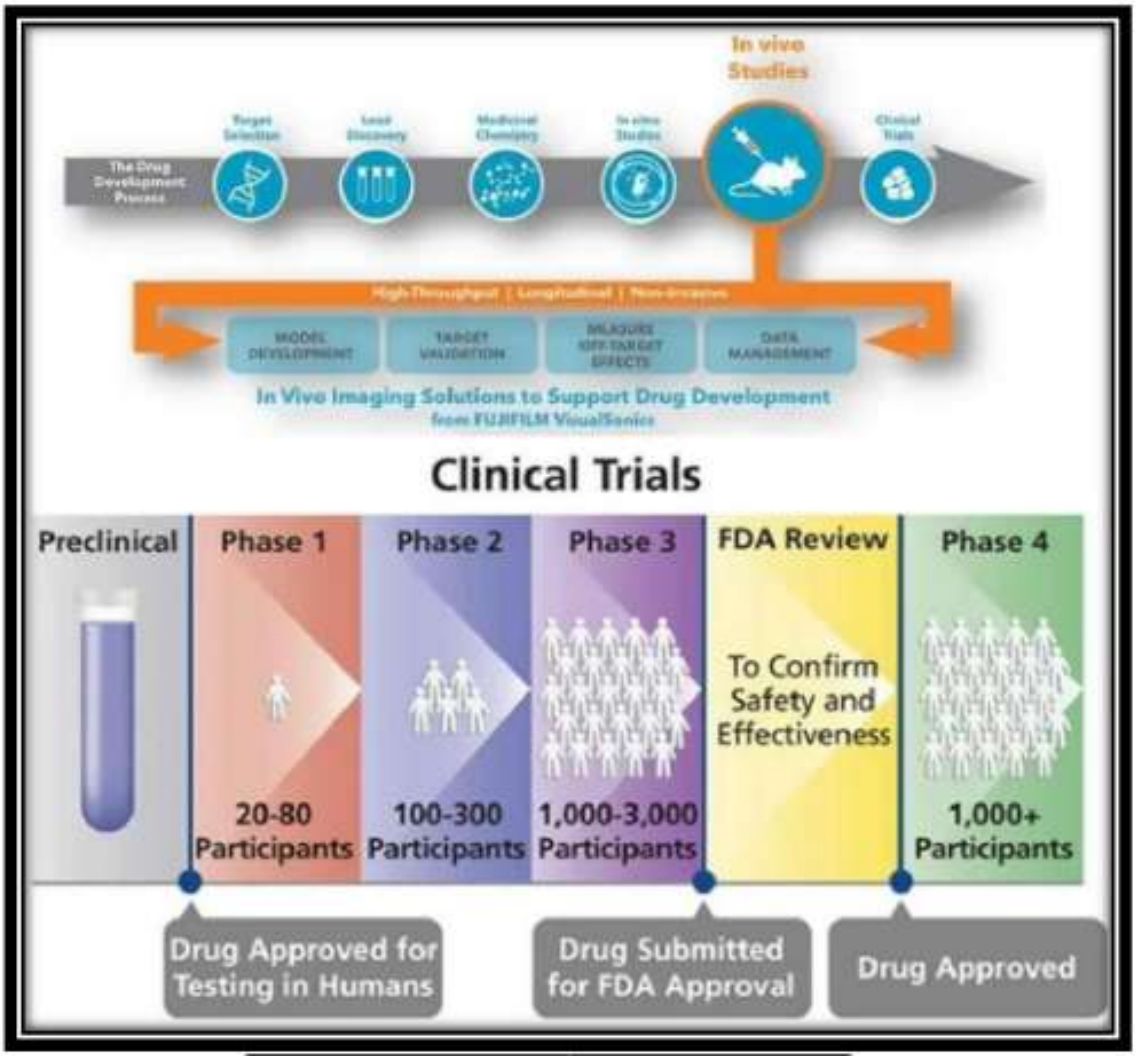

An RDP outlines the clinical, nonclinical, and chemistry, manufacturing, and controls (CMC) activities, required at each stage of development, to support the NDA and the timeline to complete them. The RDP should also outline the time points when the applicant will meet with the FDA to discuss the ongoing development of the drug and receive feedback from the FDA regarding the plan. The RDP is usually prepared by the regulatory affairs representative on the development team. In addition to knowing the contents of applicable laws, regulations, and guidance documents, this individual should have an understanding of the disease or condition being investigated, the affected patient population, the approved drugs available to treat patients with the disease or condition, and the basis of approval for those drugs. It is also the regulatory representative's responsibility to know the expectations of the FDA division that will be reviewing the NDA.

The development of the RDP will depend upon the type of NDA being submitted. For the purposes of this chapter, we will discuss the contents of a full or complete NDA. This type of NDA is referred to as a 505(b)(1) application. This type of NDA contains full reports of investigations of safety and effective- ness to support approval. The investigations that support this type of approval are conducted by or for the applicant. If the investigations are conducted by another party, the applicant can obtain a right of reference to use the information in sup- port of the NDA.18 The following are additional types of NDAs that may require different content, and thus a change to the RDP.[6] [7]

This application is one described under Section 505(b)(2) of the FD&C Act as an

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application for which one or more of the investigations relied upon by the applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted" [21 USC 355(b)(2)]. This provision permits the FDA to rely on a previous finding of safety and effective- ness that led to the approval of an NDA or on data not developed by the applicant such as a published literature. 505(b)(2) applications are submitted under section 505(b) of the Act and are therefore subject to the same statutory provisions that govern 505(b)(1) applications that require, among other things, "full reports" of safety and effectiveness. Abbreviated NDA (ANDA). An ANDA is described under Section 505(j) of the Act as an application that contains information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use, among other things to a previously approved application [the reference listed drug (RLD)]. ANDAs do not contain clinical studies as required in NDAs but are required to contain information establishing bioequivalence to the RLD. In general, the bioequivalence determination allows the ANDA to rely on the Agency's finding of safety and efficacy for the RLD. Supplemental NDA (SNDA). According to the FD & C Act, the term supplement means a request to the Secretary of Health and Human Services to approve a change in a human drug application which has been approved. The applicant will submit an NDA for each new indication or claim to be added to the product label.

There are many sources of information that a regulatory person can access to develop the RDP. In addition to the laws, regulations, and guidance documents presented earlier, the FDA Website provides a vast amount of information such as approval summaries, approved product labeling, and transcripts of Advisory Committee meetings that can guide the development of the RDP. By accessing the Drugs @ FDA section of the Website, the approval history and approval documents for most drugs approved by the FDA can be seen. This can provide insight into nonclinical and clinical trial designs, and endpoints to support approval of drugs with similar indications. In addition the site provides the approval letters, which may provide insight into required postmarketing studies, and approved labeling. By accessing the transcripts from Advisory Committee meetings, a regulatory professional can obtain an understanding of the FDA's concerns about medications to treat a proposed indication or the use of medical criteria to assess benefit. The reader will see the FDA's questions that are posed to a panel of experts and the responses of the experts, which the FDA usually follows.

Additional sources of information to support the development of the RDP include patient disease organizations such as The National Organization for Rare Diseases (NORDs). NORD is a unique federation of voluntary health organizations dedicated to helping people with rare "orphan" diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and service. This type of Website may provide insight into the concerns of patients, how the disease affects their life or health-care providers, and what are the hurdles to treating a patient. The FDA will listen to these concerns when making an approval decision about a drug.[8] Another valuable source of information is review articles that are writ- ten by members of the FDA review teams describing the approval of a drug. Using PubMed, a regulatory professional can search for articles summarizing the approval of a similar medication. This type of an article will provide insight into the type of studies that supported approval, the clinical benefit provided to the patients, and how the review team determined that the drug demonstrated a favorable benefit-risk profile in the proposed patient population.

Using all of the information above, a regulatory professional can develop an RDP to advise the development team about the types of nonclinical, clinical, and CMC activities required to support the NDA and the timeline to conduct those activities during development process. Based upon the study population being treated and the results of studies, the regulatory professional may recommend that the team apply for Orphan status, Fast-Track Designation, accelerated approval, or priority review. All of these mechanisms will provide advantages to the applicant filling an NDA. For example, Orphan status would exempt the applicant from paying the PDUFA fee, Fast-Track Designation would allow for rolling review of the NDA, accelerated approval would allow marketing of the drug while confirmatory studies are being completed, and priority review if granted would

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require the FDA to complete the review of the NDA in eight months versus 12 months.

The RDP should include timelines to meet with the FDA (see Chapter 4) at each stage of clinical development to discuss issues and ensure that the evidence necessary to support a marketing approval will be developed Prior to submitting an NDA, the applicant should schedule a pre NDA meeting with the FDA. The purpose of a pre-NDA/BLA meeting is to discuss format and content of the anticipated application, including labeling and risk evaluation and mitigation strategy (REMS), if applicable, presentation of data, dataset structure, acceptability of data for submission, and the projected submission date of the application. The meeting should be held sufficiently before the planned submission of the application so that the applicant has time to incorporate the feedback received from the FDA. In general, the meeting should not occur less than two months prior to the planned submission.20

Given the vast number of activities that need to be completed prior to submit- ting an NDA, a careful planning should be an ongoing practice throughout the development process for a new drug. A detailed RDP will improve the success of the NDA filing and successful review of the application.[9]

FORMAT AND CONTENT OF THE NDA

The presentation and organization of the NDA can be instrumental in gaining a positive approval decision from the FDA. By presenting the information and data in a clear and organized manner, an applicant can direct the reviewer to the required information that will support the claims contained in the proposed labeling and possibly decrease the time needed to review the application .Until the reauthorization of PDUFA V, there is no regulation that required the submission of an NDA in any particular format. However, the FDA published numerous guidance documents regarding the format, assembly, content, and submission of the NDA using the eCTD format. Therefore, this was the expected format and media for submission of an NDA to the FDA. format directs the reviewer where to find information, and the electronic publication facilitates review of the vast amount of information.

The CTD is an agreed-upon format for the preparation of a well-organized application that will be submitted to regulatory authorities to support the registration of pharmaceuticals for human use. This format was developed and agreed. Upon by the parties involved with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The ICH is a joint initiative involving both regulators and research-based industry representatives of the European Union, Japan, and the United States. ICH's mission is to achieve greater harmonization to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource manner.

The initial goal of the ICH initiative was to harmonize the technical requirements for the registration of pharmaceuticals. By establishing the CTD format, the organization of the technical requirement sections in the CTD has now been harmonized. The content of the CTD is determined by regulations and discussions with regional regulatory authorities. In our case, a sponsor may decide to use the CTD format, but the contents of the NDA are dictated by the regulations discussed earlier, especially 21 CFR Part 314.50.

By eliminating the need to prepare multiple region-specific sub- missions, applicants
can save valuable resources and reduce costs. In addition, the use of the CTD format can prevent the omission of critical data or analyses that could cause the FDA to refuse to file the application.

Module 1: is not part of the CTD because it is not harmonized. The contents of this module differ because it contains region-specific information.

Modules 2: through 5 are harmonized and contain the technical information required in a registration submission. Since the reauthorization of PDUFA V will mandate the submission of an NDA as an eCTD, the regulatory content of an NDA will be presented in the format of the CTD. Readers are reminded that the content of each NDA is defined by regulation and agreements made with the reviewing division at the FDA, prior to submission.[10]

MODULE 1: ADMINISTRATIVE AND PRESCRIBING INFORMATION

For an NDA submission in the United States, this module contains all of the administrative and labeling documents required for the submission. This includes application forms, administrative documents, and REMS if needed.

Module 1: also contain a comprehensive table of contents (TOC) and the index for the

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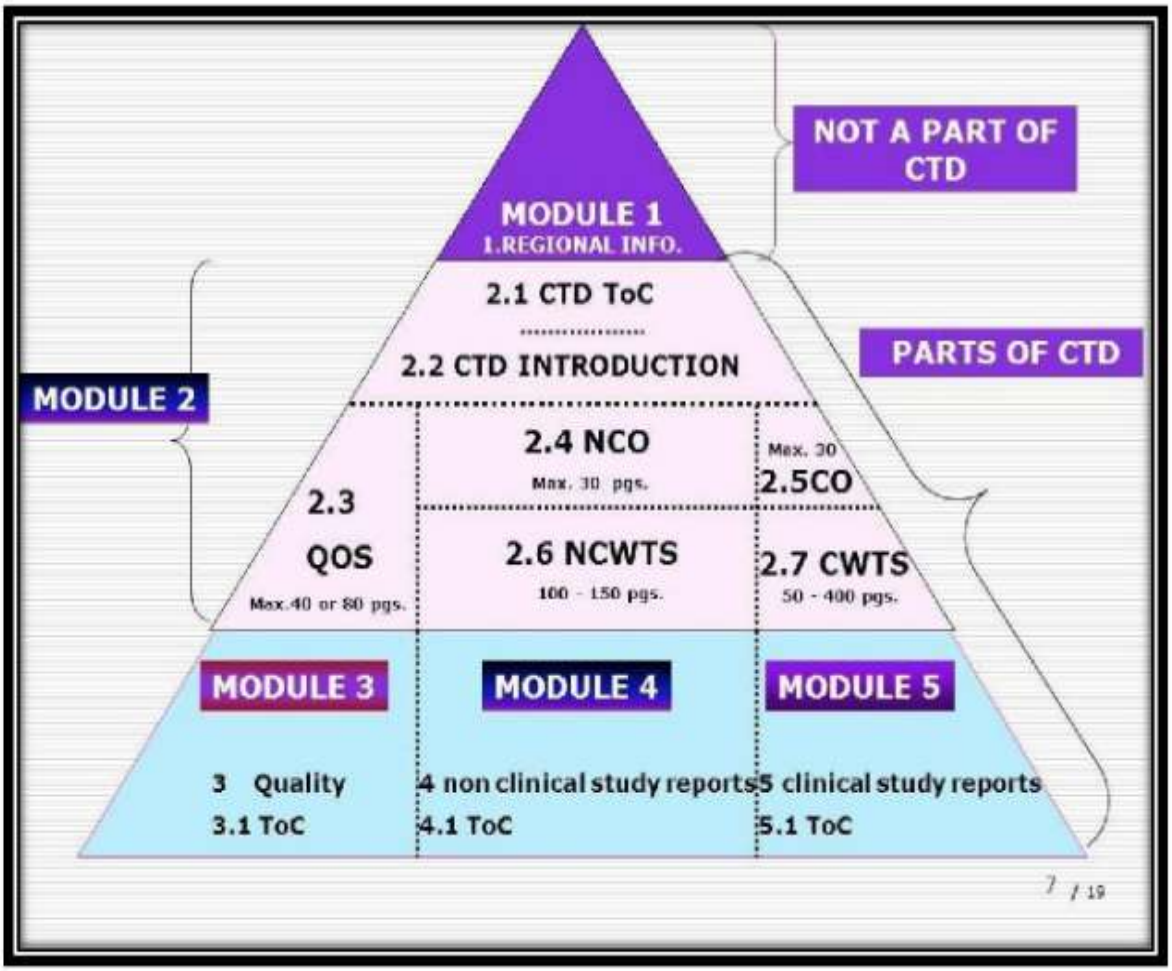

Section 1.1: Forms-Application Form [21 CFR 314.50(a)]

Each applicant is required to submit a signed Form FDA 356h,26 This form is published by the FDA and updated periodically. The form contains information about the sponsor, the drug, and the proposed indication, as well as a checklist of the items contained in the NDA. By signing the form, the responsible official or of the NDA certifies that all information in the application is true and accurate and, in addition, that the applicant will comply with a range of legal and regulatory requirements. If the applicant is not located in the United States, the form must name an agent with a US address.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

APPLICATION TO MARKET A NEW OR ABBREVIATED NEW DRUG OR BIOLOGIC FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: December 31, 2013
See PRA Statement on page 3.

1. Date of Submission *(mm/dd/yyyy)*

APPLICANT INFORMATION

2. Name of Applicant

3. Telephone Number *(Include country code if applicable and area code)*

4. Facsimile (FAX) Number *(Include country code if applicable and area code)*

5. Applicant Address

Address 1 *(Street address, P.O. box, company name c/o)*

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City | State/Province/Region

Country | ZIP or Postal Code

U.S. License Number if previously issued

6. Authorized U.S. Agent Name, Address, Telephone and FAX Number *(If applicable)*

U.S. Agent Name

Address 1 *(Street address, P.O. box, company name c/o)*

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City | State

ZIP or Postal Code

Telephone Number *(Include area code)*

FAX Number *(Include area code)*

PRODUCT DESCRIPTION

7. NDA, ANDA, or BLA Application Number

8. Supplement Number *(If applicable)*

9. Established Name *(e.g., proper name, USP/USAN name)*

10. Proprietary Name *(Trade Name) (If any)*

11. Chemical/Biochemical/Blood Product Name *(If any)*

12. Dosage Form | 13. Strengths | 14. Route of Administration

15. Proposed Indication for Use

Is this indication for a rare disease (prevalence <200,000 in U.S.)? ☐ Yes ☐ No

Does this product have an FDA Orphan Designation for this indication? ☐ Yes ☐ No

If yes, provide the Orphan Designation number for this indication:

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APPLICATION INFORMATION

16. Application Type *(Select one)* ☐ New Drug Application (NDA) ☐ Biologics License Application (BLA) ☐ Abbreviated New Drug Application (ANDA)

17. If an NDA, identify the type ☐ 505 (b)(1) ☐ 505 (b)(2)

18. If a BLA, identify the type ☐ 351 (a) ☐ 351 (k)

19. If a 351(k), identify the biological reference product that is the basis for the submission.
Name of Biologic: _____ Holder of Licensed Application: _____

20. If an ANDA, or 505(b)(2), identify the listed drug product that is the basis for the submission.
Name of Drug: _____ Application Number of Relied Upon Product: _____
Indicate Patent Certification: ☐ P1 ☐ P2 ☐ P3 ☐ P4 ☐ Section viii - MOU ☐ Statement of no relevant patents

21. Submission *(Select one)* ☐ Original ☐ Labeling Supplement ☐ CMC Supplement ☐ Efficacy Supplement ☐ Annual Report
☐ Product Correspondence ☐ REMS Supplement ☐ Post Marketing Requirements or Commitments ☐ Periodic Safety Report
☐ Other *(Specify)*: _____

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22. Submission Sub-Type ☐ Presubmission ☐ Amendment ☐ Initial Submission ☐ Resubmission

23. If a supplement, identify the appropriate category. ☐ CBE ☐ Prior Approval (PA) ☐ CBE-30

24. Does this submission contain only pediatric data? ☐ Yes ☐ No

25. Reasons for Submission

26. Proposed Marketing Status *(Select one)* ☐ Prescription Product (Rx) ☐ Over-The-Counter Product (OTC)

27. This application is *(Select one)* ☐ Paper ☐ Paper and Electronic ☐ Electronic

28. Number of Volumes Submitted

29. Establishment Information *(Full establishment information should be provided in the body of the application.)*

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, registration number (FEI), MF number, Establishment DUNS number, and manufacturing steps and/or type of testing (e.g., final dosage form, stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Establishment Name

Address 1 *(Street address, P.O. box, company name c/o)*

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City | State/Province/Region

Country | ZIP or Postal Code

Registration (FEI) Number

MF Number

Establishment DUNS Number

Manufacturing Steps, Type of Testing, and Site Contact Information

Is the site ready for inspection? ☐ Yes ☐ No

If No, when will site be ready? *(mm/dd/yyyy)*

Continuation Page for #29

30. Cross References (List related BLAs, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, MAFs, and DMFs referenced in the current application.)

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31. This application contains the following items *(Select all that apply)*

☐ 1. Index ☐ 2. Labeling *(Select one)*: ☐ Draft Labeling ☐ Final Printed Labeling ☐ 3. Summary *(21 CFR 314.50 (c))*

☐ 4. Chemistry Section
- ☐ A. Chemistry, manufacturing, and controls information *(e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)*
- ☐ B. Samples *(21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)*
- ☐ C. Methods validation package *(e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)*

☐ 5. Nonclinical pharmacology and toxicology section *(e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)*

☐ 6. Human pharmacokinetics and bioavailability section *(e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)*

☐ 7. Clinical microbiology section *(e.g., 21 CFR 314.50(d)(4))*

☐ 8. Clinical data section *(e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)*

☐ 9. Safety update report *(e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)*

☐ 10. Statistical section *(e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)*

☐ 11. Case report tabulations *(e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)*

☐ 12. Case report forms *(e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)*

☐ 13. Patent information on any patent that claims the drug/biologic *(21 U.S.C. 355(b) or (c))*

☐ 14. A patent certification with respect to any patent that claims the drug/biologic *(21 U.S.C. 355 (b)(2) or (j)(2)(A))*

☐ 15. Establishment description *(21 CFR Part 600, if applicable)*

☐ 16. Debarment certification *(FD&C Act 306 (k)(1))*

☐ 17. Field copy certification *(21 CFR 314.50 (l)(3))*

☐ 18. User Fee Cover Sheet *(PDUFA Form FDA 3397, GDUFA Form FDA 3794, BsUFA Form FDA 3792, or MDUFMA Form FDA 3601)*

☐ 19. Financial Disclosure Information *(21 CFR Part 54)*

☐ 20. Other *(Specify)*: _____

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CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to, the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state, and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge, are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

32. Typed Name and Title of Responsible Official or Agent signing this form	33. Date *(mm/dd/yyyy)*

34. Telephone Number *(Include country code if applicable and area code)*	35. FAX Number *(Include country code if applicable and area code)*	36. Email Address

37. Address

Address 1 *(Street address, P.O. box, company name c/o)*	
Address 2 *(Apartment, suite, unit, building, floor, etc.)*	
City	State/Province/Region
Country	ZIP or Postal Code

38. Signature of Applicant's Responsible Official Sign	39. Signature of Authorized U.S. Agent Sign

The information below applies only to requirements of the Paperwork Reduction Act of 1995.

The burden time for this collection of information is estimated to average 24 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

DO NOT SEND YOUR COMPLETED FORM TO THIS PRA STAFF ADDRESS.

FORM FDA 356h (4/13) **Page 3 of**

Section 1.1: Forms [User Fee Cover Sheet (Form FDA 3397)]

A User Fee Cover Sheet is to be completed and submitted with each new drug or biologic product NDA. The form provides a cross reference to the user fee paid by the applicant.

Section 1.2: Cover Letter/Index [21 CFR 314.50(b)]

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The NDA index is a comprehensive TOC that enables the reviewers to quickly find specific information in this massive document. It must show the location of every section in the archival NDA by volume and page number. It should guide reviewers to data in the technical sections, the summary, and the supporting documents.

Section 1.3.2: Field Copy Certification [21 CFR 314.50(d)(1)(v)]

The NDA must include a certification statement noting that the field copy, submitted to the local FDA office, is a true copy of the CMCs section that was submitted in the archival and review copies of the application. However, FDA district offices have access to documents submitted in electronic format. Therefore, when sending submissions in electronic format, any duplicate documentation to the FDA Office of Regulatory Affairs District Office must be provided. To meet the requirements of the regulation, a letter certifying that the electronic CMC section has been submitted should be provided to the Office of Regulatory Affairs District Office and a letter certifying that the letters were submitted should be included in the NDA.

Section 1.3.3: Debarment Certification [FD&C Act 306(k)(1)]

Section 306(k)(1) of the FD&C Act requires an NDA to contain a statement certifying that the applicant did not and will not use in any capacity the services of any person debarred by the FDA. The certification statement should not use conditional or qualifying language, such as "to the best of my knowledge." The following wording is considered the most acceptable form of certification by the FDA" [Name of the applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Section 1.3.4: Financial Certification and Disclosure [21 CFR Part 54]

The NDA is required to contain information regarding all financial interests or arrangements between clinical investigators, their spouses and immediate family members, and the sponsor of the clinical trials that support the NDA.

An investigator who had financial interests to disclose is not disqualified from the application per se; a financially incented investigator should not enroll a majority of subjects nor be the principal investigator for the larger testing sites.

Section 1.3.5.1: Patent Information [21 CFR 314.50(h) and 314.53] The law requires patent information to be submitted with the NDA. An applicant is required to disclose all patent information that is related to the drug for which the NDA is being filed and to verify that the sponsor has all rights necessary to legally manufacture, use, and sell the drug, if the NDA is approved. The patent inquiry is a broad one and covers drug substance (active ingredient) patents, drug product (formulation and composition) patents, and method-of-use patents. In all likelihood, it should be signed only after review by a qualified attorney or patent agent who can provide an opinion as to the truth and accuracy of the completed form. The signature on the form called a "verification" reads thus:

The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment or supplement pending under section 505 of the Federal FD&C Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

In addition, applicants must maintain these patent statements and are required to submit updates before and after approval using Form FDA 3542(a) for each patent. We also note that there are "safe harbors" protecting a person from claims of patent infringement which apply expressly to drugs; this exemption essentially allows generic manufacturers or name-brand competitors to "jump start" the approval process by conducting required testing even though the original patent has not expired. The law reads thus:

It shall not be an act of [patent] infringement to make, use, offer to sell or sell within the United States or import into the United States a patented invention... solely for uses reasonably related to the development and submission of information under a federal law which regulates the manufacture, use or sale of drugs or veterinary biological products.

Again, because patent infringement carries criminal penalties, consulting with a qualified patent attorney or an agent is essential.

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Section 1.3.5.2: Patent Certification [21 CFR 314.50(i) and 314.52]

If the new drug is covered by a patent or patents, which the applicant(s) believe(s) to be invalid, a different procedure and format are used. Under this regulation, there is no specific form to file; there is a requirement to certify specific items, all as stated in the regulation. In this case, the patents must still be disclosed, but also, the applicant must certify under 21 CFR 314.50(i)(1)(i)(A)(4) that the patent is invalid, unenforceable, or will not be infringed, and further, the applicant is required to send a specific notice by registered or certified mail, and a return receipt requested to specified interested parties. Again the purpose is to prevent the Agency from essentially wasting its time to review an application for a drug that cannot be legally manufactured.

Section 1.12: Other Information [21 CFR 314.50(g)]

The applicant can use this item to provide additional information, requested by the FDA, as needed for the NDA.

Section 1.14: Labeling [21 CFR 314.50(e)]

The labeling section must include all draft labeling that is intended for use on the product container, cartons or packages, including the proposed package insert.

The labeling requirements are very specific and detailed. Applicants must be familiar with all regulatory requirements, especially those under Sections 21 CFR 201.56(d)(1) and

201.57. The pertinent regulation at 201.56(d)(1) mandates that the labeling must contain the specific information required under section 201.57(a), (b), and (c).

Each section of the labeling must include annotations referencing the information in the summary and technical sections of the application that support the inclusion of each statement in the labeling with respect to animal pharmacology and/or animal toxicology, clinical studies, and integrated summary of safety (ISS) and integrated summary of effectiveness (ISE0).[10][11]

MODULE 2: COMMON TECHNICAL DOCUMENT-SUMMARY (21 CFR 314.50)

- Module 2 contains a comprehensive TOC of modules 2 through 5 as well as the following overviews and summaries of the technical data in modules 3 through 5.

Section 2.2: Introduction to the Summary Documents

The introduction to the summary documents should be a one-page general introduction about the pharmaceutical product in the application. Applicants should provide information regarding the pharmacologic class, mode of action, and proposed clinical use of the drug.

Section 2.3: Quality Overall Summary

The quality overall summary should provide the reviewer with an overview of the CMC information contained in module 3.

The summary should not restate the detailed CMC information contained in module 3. Instead, the summary should address key parameters of the product and discuss how the CMC information in module 3 relates to the other modules in the submission.

Section 2.4: Nonclinical Overview

The nonclinical overview should provide an interpretation of the data, the clinical relevance of the findings cross-linked to the quality aspects of the pharmaceutical, and the implications of the nonclinical findings for the safe use of the pharmaceutical.

Section 2.5: Clinical Overview

The clinical overview should provide a succinct discussion and interpretation of the clinical findings that support the application together with any other relevant information such as pertinent animal data or product quality issues that may have clinical implications.

Section 2.6: Nonclinical Written and Tabulated Summaries

The nonclinical written and tabulated summaries should provide a comprehensive, factual synopsis of the nonclinical data.

Section 2.7: Clinical Summary

The clinical summary should provide a detailed factual summarization of the clinical information in the application.

MODULE 3: QUALITY

Module 3 contains a TOC for module 3 only and detailed data on CMC, including references.

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MODULE 4: NONCLINICAL STUDY REPORTS

Module 4 contains a TOC for module 4 only, nonclinical study reports contained in the application, and literature references.

MODULE 5: CLINICAL STUDY REPORTS

Module 5 contains a TOC for module 5 only and a tabular listing of all clinical studies, clinical study reports, and literature references.[12]

SUBMISSION AND REVIEW OF THE NDA

As discussed earlier in the chapter, one of the commitments of PDUFA V, was the implementation of a new review program (the Program) for NME-NDAs and original BLAs to promote greater transparency and increased communication between the FDA review team and the applicant. The goals of "the Program" are to increase the efficiency and effectiveness of the first review cycle and decrease the number of review cycles necessary for approval so that patients have timely access to safe, effective, and high-quality new drugs and biologics.

The revised program is a six-step review process depicted in Figure 3.4 (titled Overview of the NDA/BLA Review Process Major Milestones and Timelines). Two of the six steps, pre submission activities and post action feedback to the applicant, occur outside of the review time frame that has been extended by two months. The timelines for NMEs and BLAs that fall under PDUFA V's "program" review model are 10 months for standard applications and six months for priority reviews from the 60-day filing date or 12 months and eight months, respectively, from the date of submission of the application.

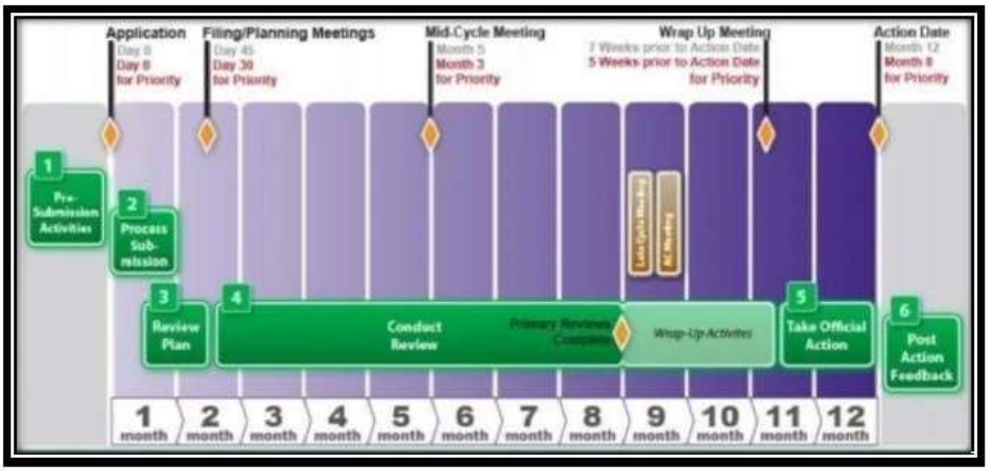
STEP 1: ENSURE READINESS FOR APPLICATION THROUGH PRESUBMISSION ACTIVITIES

The first step in the new process involves multiple activities that applicants can do to improve the quality and content of their NDA/BLA application prior to its submission .

During this time, the applicant should be requesting a pre-NDA meeting. As discussed earlier, the purpose of this meeting is to discuss format and content of the anticipated application, including labeling, REMS, if applicable, presentation of data, dataset structure, acceptability of data for submission, and the projected submission date of the application.

In addition to the pre-NDA meeting, applicants are also encouraged to sched- ule an electronic pre-submission meeting with the reviewing division to address the technical aspects of the submission. The focus of the meeting is on navigation, formatting of electronic files, and layout of the application, 20

To prepare for the meetings, the applicant will need to submit a briefing document containing questions and supportive information for the division to review. The applicant may submit technical information such as the results of pivotal studies and proposed datasets, highlights of potential problems such as quality issues or safety signals, or a draft index of the NDA submission and ask the Agency how to address the issues in the NDA submission.



One of the goals of PDUFA V is to improve the first cycle review of applications. As such the applications are expected to be complete at the time of filing. However, during the pre submission meeting, the FDA and the applicant may reach agreement on the submission of limited

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application components no later than 30 days after the submission of the original application. Examples of application components that may be appropriate for delayed submission include updated stability data (e.g., 15-month data to update 12-month data submitted with the original submission) or the final audited report of a preclinical study (e.g., carcinogenicity) where the final draft report is submitted with the original application.20 All agreements should be summarized in the minutes of meeting from the FDA.

Pre submission meetings between the applicant and the FDA, in conjunction with good FDA- industry IND interactions will help ensure that the NDA application will be complete and file able.

STEP 2: PROCESS SUBMISSION

The review process for an NDA application begins when the NDA is submitted to the FDA. However, the PDUFA time clock starts 60 days following the submission of an NDA. The NDA should be submitted to the FDA on physical media, or preferably through the Electronic Submission Gateway at the FDA.

The regulatory project manager (RPM) at the FDA will begin by ensuring that the PDUFA fee was paid or exempted. The PDUFA fee must be paid within 5 days of submitting the NDA, or the RPM will send the applicant an "unacceptable for filing" letter. If the fee was paid, the RPM is responsible to ensure that the NDA is administratively complete and compliant with regulatory requirements. Remember that the application must be complete unless the applicant had a previous agreement with the FDA. If complete, the application is distributed to the discipline team leaders (DTLs) that determine if a reviewer assignment is needed. If so, a reviewer from each discipline is assigned to review the NDA and receives a copy of the NDA by day 14. The RPM is responsible to send the applicant a letter acknowledging the receipt of the NDA by day 14.[13]

STEP 3: PLAN REVIEW OF THE APPLICATION

During the first 60 days following the submission of the NDA, the FDA has to (1) determine the file ability of the application and (2) plan the review. The review team conducts an initial assessment of the NDA/BLA and associated labeling to identify and address any potential filing issues. The RPM will convey any potential filing issues to the applicant as soon as possible to promote resolution. Within 14 days, a tentative decision should be made if the NDA will receive priority designation. Within 45 days of receiving the application, the FDA may request an applicant orientation presentation meeting. The purpose of this meeting is to have the applicant orient the review team to the application. During the filing meeting, day 45 of the review or day 30 for priority reviews, the review team will decide if the NDA is fileable, identify significant review issues, and determine if the NDA review will be classified as priority or standard. There are three potential filing decisions:
(1) file the application, (2) potentially refuse to file the application, and (3) refuse to file the application. The decision is sent to the applicant by day 60 in a filing notification letter.

If the NDA is deemed fileable, the RPM will The RPM will then prepare a filing communication letter (74-day letter) that informs the applicant of deficiencies, filing review issues, and the planned time-line, including the internal mid-cycle meeting, for review activities. The letter must include the target dates for transmitting initial labeling and postmarketing requirements (PMRs) and PM commitments (PMCs) comments and final review designation (within 60 days for priority review). This letter will also include preliminary plans for an Advisory Committee meeting to discuss the application.

Initiate a planning meeting. The purpose of the planning meeting is to organize review tasks, minimize review over- lap across review disciplines, and establish an agreed-upon internal review time- line, including a schedule of team meetings and deliverables. 20 The review team will determine if any consultant reviewers are needed, establish a plan for labeling review, and finalize the need for an Advisory Committee.

The review team will also identify sites to conduct inspections on good laboratory practices (GLPs), good clinical practices (GCPs), and good manufacturing practices (GMPs). The FDA's program to inspect sites for GLPs and GCPs is called the bioresearch monitoring program (BIMO). In preparation for an inspection, the applicant can review the BIMO procedures manual and have the information ready when the FDA inspector arrives.

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Step 4: Conduct Scientific/Regulatory Review Of The Application

During the review phase, the reviewers from each discipline conduct their in-depth reviews. Reviewer's requests for additional information or analysis will be communicated to the applicant through the RPM.A mid-cycle meeting is held by month 5 for standard reviews and month 3 for priority reviews. The objectives of this meeting are to present the status of the review and any key findings, confirm the decision regarding the need for an Advisory Committee, identify approvability issues, and discuss labeling and the need for an REMS. The mid-cycle meeting also gives the review team a chance to get feedback from signatory authorities and other discipline directors. The RPM will provide the applicant with an update on the status of the review within two weeks of the mid-cycle meeting. For PDUFA V "program" reviews, a late-cycle meeting is held between the review team and the applicant. An additional two months is available for PDUFA V "program" applications to address complex review issues and attempt to remedy minor problems with the application.

STEP 5: TAKE OFFICIALACTION ON THE APPLICATION

Based on the signatory authority's review of the action package and on discussions with the review team, the signatory authority determines the action to be taken on the application. The final action decision is conveyed to all team members.

STEP 6: PROVIDE POSTACTION FEEDBACK TO THE APPLICANT

The focus of this activity is to learn from the review experience. This optional meeting can take place as either an end-of-review conference, typically held following an action other than an approval, and/or a post action feedback/lessons learned meeting. These two meetings can be combined into a single meeting if appropriate.[14]

II. CONCLUSION

The NDA is the capstone of drug development. It is a process that deserves intense scrutiny; it balances the need for drugs whose benefits outweigh the risks of their side effects. The public hopes that the Agency "gets it right"; but ultimately, the decisions are reflective of the science, the data, and the uncertainties presented by the human condition.

As new discoveries and technologies permit new therapies and approaches to curing, mitigating, and diagnosing disease and the public demand for even more rapid access to safe medications, increases, we can anticipate that the rules and regulations governing the Agency will continue to evolve

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