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A Review on New Drug Application (NDA) and General Consideration in Pharmaceutical Industry

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ABSTRACT

In the pharmaceutical industry the course is designed to give you the skills that have taken many experienced The New Drug Application (NDA) is an application submitted to U.S.FDA for permission to market a new drug product in the United States. The New Drug Application (NDA) is an application submitted to U.S.FDA for permission to market a new drug product in the United States. The components of any NDA are a function of the nature of the subject drug and the information available to the applicant at the time of submission. The form to use for either NDA or ANDA is Form FDA-356h, Application to Market a New Drug for Human Use or as an Antibiotic Drug for Human Use. The international regulatory authorities under consideration are WHO, USFDA, MHRA, and Australian TGA. The standard institutions give the economical background for development and transferring technologies, ISI, ISO, BISS and ASTM. To legally gather this data on safety and effectiveness in the U.S., the maker must first obtain an Investigational New Drug (IND) designation from FDA.

Keywords: Regulatory authority, ANDA, NDA, IND.

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INTRODUCTION

To legally gather this data on safety and effectiveness in the U.S., the maker must first obtain an Investigational New Drug (IND) designation from FDA. The documentation required in an NDA is supposed to tell the drug's whole story, including,

- What happened during the clinical tests?
- What the ingredients of the drug formulation are,
- The results of the animal studies,
- How the drug behaves in the body, and
- How it is manufactured, processed and packaged.

Once approval of an NDA is obtained, the new drug can be legally marketed starting that day in the U.S.

FUNDAMENTALS OF NDA SUBMISSIONS [4, 5, 6]

- Although the quantity of information and data submitted in NDAs can vary significantly.
- The components of any NDA are a function of the nature of the subject drug and the information available to the applicant at the time of submission.
- The form to use for either NDA or ANDA is Form FDA-356h, Application to Market a New Drug for Human Use or as an Antibiotic Drug for Human Use.

NDA CLASSIFICATIONS [5, 6, 7, 8]

CDER classifies new drug applications with a code that reflects both the type of drug being submitted and its intended uses.

- New Molecular Entity
- New Salt of Previously Approved Drug
- New Formulation of Previously Approved Drug
- New Combination of Two or More Drugs
- Already Marketed Drug Product – Duplication by new manufacturer
- New Indication for Already Marketed Drug, including switch in status to OTC (conversion of prescription drug to OTC)
- Already Marketed Drug Product without previously Approved NDA.

NDA REQUIREMENTS [3, 5, 7]

- Content and format of application
- Formatting, assembling and submitting new drug and antibiotic applications
- NDA summary format and content

- NDA technical sections
- Abbreviated new drug application

(I) Content and format of application:

Although the exact requirements are a function of the nature of a specific drug, the NDA must provide all relevant data and information that a sponsor has collected during the product's research and development.

(II) Formatting, assembling and submitting new drug and antibiotic applications:

A. Application format:

The NDA regulations require the submission of

1. Archival copy

2. Review copy

1. Archival copy:

This is a complete copy of an application submission and is intended to serve as a reference source for FDA reviewers. This contains information which not contained in the review copy

2. Review copy:

It is divided into five (or six) sections containing technical and scientific information required by FDA reviewers. Each of sections of review copy is separately bound. It should be provided with following:

- A copy of cover letter.
- A copy of application form (FDA 356h)
- A copy of overall summary
- A copy of index to the entire application
- An index to the specific review section
- Both copies are submitted in hard copy.

I. Assembling the application [5, 7, 9]:

Folders: Because of the procedure used at the FDA to file and retrieve material from the document rooms where applications are kept, it is necessary that applicants use the colored folders to bind the archival copy and each technical section. The cover of each folder should bear the NDA number (if known), name of applicant and name of drug product.

Paper size and binding: All applications must be bound on the left side of the page using the Unite States standard size loose leaf page. (8.5″*11″).

Pagination: All pages in the application must be numbered and numbering of review copy pages should be same as the numbering of corresponding pages in archival copy.

Volume size and identification: Volume submitted in hard copy form should be no more than 2 inches thick.

Packing carton: The box size of 14″*12″*9.5″ is recommended for shipment of applications to FDA. Because ANDAs are handled and stored separately, smaller boxes may be appropriate for them.

Supplements, Amendments and Post marketing Reports: The submission format for amendments to pending applications and supplements to approved applications will be same as an original application. Each submission will consist of two copies: a complete archival copy and an appropriately segmented review copy. Amendments, supplements, resubmissions annual reports and other correspondence concerning full applications should be addressed to appropriate FDA reviewing divisions.

Table 1: FDA does not regulate following consumer products [6]

Restaurants & Grocery Stores	Pesticides	Health & Insurance
Country Health Department	USFDA, EPA, USPDA	FDA Not Regulate

II. Application content [2, 4, 6]

Archival copy

The archival copy should confirm the agreement between the FDA and the applicant. The letter should cite any relevant meetings by date and topic, and identify one or more persons the FDA may contact regarding the application. The letter may include any other information the applicant wishes to convey to the FDA about the application.

- The archival copy is required to contain the following:
- Application form (FDA 356h) it serves as a cover sheet for the application, contains basic identifying information about the applicant and the drug product.
- The application form, as well as the index and the summary should be bound together in a single volume. Patent information on the applicant's drug and a patent certification with respect to the drug should be submitted on a separate piece of paper attached to the application form itself.

NDA SUMMARY FORMAT AND CONTENT:

Summary should provide sufficient detail. Data should be provided in tabular or graphical form,. Summary should be between 50-200 pages.

A. Package insert:

This section includes proposed text of the labeling for the product. The proposed text of the package labeling must be annotated by reference to volume and page number to the information in the summary and in technical sections of the applications.

B. Pharmacological class, scientific rationale, intended use and potential clinical benefits:

A brief statement should be included to identify the pharmacological class of the drug, the scientific rationale for the drug, its intended use, and its potential clinical benefits.

C. Chemistry, Manufacturing and Controls:

This summary must provide overview of the drug substances and the drug product.

Drug substance:

It includes description about of drug substance, physical and chemical characteristics and stability of the drug substance.

Drug product:

It includes information about:

a. Composition and dosage form
b. Name and address of manufacturer
c. Container and closure system
d. Stability
e. Specifications for drug product and test methods to assure the specifications

D. Foreign Marketing History:

If the product is marketed outside the U.S., regardless of the dosage form, strength, salt, ester, or complex of the drug, the marketing history should be provided. This should include a list of countries in which drug product is marketed, with dates of marketing, if known. It must also include a list of any countries in which the drug has been withdrawn for any reason relating to safety or efficacy. Specific reason for withdrawal should be given.

E. Nonclinical Pharmacology and Toxicology Summary:

It includes information about:

1. Pharmacology studies
2. Acute toxicity studies
3. Multi dose toxicity studies
4. Carcinogenicity studies
5. Special toxicity studies
6. Reproduction studies
7. Mutagenicity studies

8. ADME studies

F. Human Pharmacokinetics and Bioavailability Summary:

It includes brief description about bioavailability study of drug, pharmacokinetic characteristic of active ingredient and dissolution profile of drug.

G. Microbiology Summary:

It provides summary of results of the microbiologic studies conducted with anti-infective and antiviral drug. This includes mechanism of action, antimicrobial spectrum of action and mechanism of resistance to the drug.

H. Clinical Data Summary and Results of Statistical Analysis:

It is the basis of efficacy and safety that will determine an NDA approval. The Clinical Data Summary and Results of Statistical Analysis are divided into several parts as described below:

- Clinical pharmacology
- Overview of Clinical Studies
- Controlled Clinical Studies
- Uncontrolled Clinical Studies
- Other studies and Information
- Safety summary (general Safety Conclusions).

NDA TECHNICAL SECTIONS:

This includes brief description of the following sections.

A. Chemistry, Manufacturing and Controls:

It is the most critical portion of NDA or ANDA .This section must fully describe the composition of the drug substance (active ingredient), and its synthesis (or isolation) and purification, as well as applicable process controls, specifications, and analytical test methods.

B. Nonclinical Pharmacology and Toxicology:

It provides a description or summary of all animal and in-vitro studies with the drug.

1. Pharmacology Studies:
2. Acute Toxicity Studies:
3. Sub chronic/Chronic/Carcinogenicity Studies:
4. Special Toxicity Studies
5. Reproduction Studies
6. Mutagenicity Studies
7. ADME Studies

C. Human Pharmacokinetics and Bioavailability Section:

1. For a new chemical entity (NCE), it is desirable to determine its bioavailability and pharmacokinetics from the dosage form, except that for certain dosage forms (e.g., iv solutions) 100% bioavailability may be assumed.
2. For solid oral dosage forms (e.g., capsule or tablet) a bioequivalence study is often necessary to demonstrate that formulation proposed for marketing is bioequivalent to whatever formulations may have been employed in early clinical trial.
3. The summary should include pharmacokinetic parameter like Cmax, Tmax, kel, Vd, plasma and renal clearance and urine excretion.

D. Microbiology:

This section is of major importance for anti-infective drugs and includes data on the biochemical basis of the drug's action and its antimicrobial spectra; any known mechanisms of resistance to the drug; and clinical laboratory methods.

E. Clinical Data Section:

It is the most important and most complicated section of an NDA. It is the part that provides the safety and efficacy data on the drug for its intended use.

F. Outline of Clinical Section:

It includes the following aspects:

1. List of investigators; List of INDs and NDAs
2. Background / Overview of clinical investigations
3. Clinical pharmacology
4. Controlled clinical studies
5. Uncontrolled clinical studies
6. Other studies and information
7. Integrated summary of efficacy
8. Integrated summary of safety
9. Drug abuse and over dosage information
10. Integrated summary of benefits and risk of drugs

G. Samples, Methods Validation and Labeling:

- Samples should not be submitted to the FDA with the application. The reviewing chemist will contact the applicant and provide the laboratory address where samples should be sent.
- The applicant should prepare four representative samples in sufficient quantity to permit FDA to perform each test described in the application three times to determine whether

the drug substance and drug product meet the specification given in the application.

- The archival copy of an application is required to contain copies of the label and all labeling proposed for the drug product. Methods validation data must be provided in triplicate because copies are forwarded to two FDA laboratories.

H. Case Report Forms and Tabulations:

The sponsor must submit data tabulations from each Phase II and Phase III study and also the case study report form for every clinical trial patient who died or withdrew from the study because of an adverse event.

I. Patent Information:

Information must be submitted regarding any patent held by the sponsor that covers the drug substance, formulation, and composition of the drug product, or method of use. Upon approval of the NDA, this information is published in the FDA's Orange Book (known formally as Approved Drug Products with Therapeutic Equivalence Evaluations) and serves as a guide to firms wishing to develop generic copies of the innovator's product.

J. Patent Certification.

DATA PRESENTATION FOR FDA SUBMISSION [1, 2, 3, 7]

Followings are the ways to present data that facilitate NDA review of submission.

(I) Text exposition

(II) Tabular presentation

(I) Text exposition:

A. Content:

1. Most NDA submission contains enormous amount of data, which cannot be presented entirely within the body of a document. Although the data collected for individual patient may be important, critical judgment must be exercised in the selection of key data for presentation and discussion within a given document.

2. Data necessary for the development of specific thesis should be presented within the body of a document rather than placed into remote appendix which will impede the review.

3. Less important data can be summarized briefly and placed in appendices.

4. Data which add nothing to the evaluation of safety or effectiveness of therapeutic agent, need not be presented at all.

B. Tone:

The tone of the text should be formal without being stilted. Avoid legal language on the one hand and colloquial or informal language on the other.

C. Conciseness:

Following are the way of making NDA submission more concise.

1. Keep the language simple and straightforward. Simple language is not unscientific; rather it promotes clear and fast understanding. Edit out inflated language. For example,-"prior to the initiation of the study" can be changed to much simpler "before the study began".
2. Use acronyms and initialisms to speed up the flow of the text if they are easily recognized and have been spelled out at first mention. Those that may be confused with another used in the samedocument should be spelled out.
3. Eliminate redundancies. A careful review of the text will find many words, phrases and even sentences that can be omitted. Sentences can often be combined by deletion of redundant phrases, thus improving the flow of text.

D. Correctness:

1. The textual presentation should agree with tabular data in the document; in turn, the tabulardata should agree with the data source.

2. When lack of agreement between in-text data and source documents is found, the reviewerwill have to spend more time in evaluating the raw data to be sure of conclusion.

E. Consistency:

Consistent punctuation, capitalization, abbreviations, and other styling conventions are much desired in any document.

F. Clarity:

1. The FDA reviewer should be able to read an application easily and expeditiously. If a particular document is not clear, then FDA reviewer will have the problem for understanding it.

2. Clarity is facilitated by careful attention to the following.

Punctuation

Sentence structure and lengthMisplaced modifiers Parallelism

G. Outline of sections and subsections:

The clear relationship of one section with another is critical to the review of a document. If no definite structure is apparent, the reviewer will become lost. The decimal system is a very popular outlining system; it is easy to use and can be set up automatically in current word processing software application. For e.g., 3.1.2.1.2.1.1.1 is a subsection of 3.1.2.1.2.1.1.

H. Indenting:

Avoid indenting large sections of the text. Most text should be flush to the left margin with appropriate headers to identify the section. Generally indenting with bullets is useful to break large sections of text.

TABULAR PRESENTATION:

In-text tables should be used to simplify the presentation and substantial reduction in text. Information from tables should not be repeated in the text except as a part of concluding statement about the tabular data.

A. Title:

All tables require concise but descriptive title. Sequence of tables that are similar should identify their differences in the title, such as at the end of the title after a colon. (Treatment related adverse events: by Age…, by Sex…, by Race).

B. Data source:

Every table should identify the data source contained in it. This is usually done in the footnote to the table (data source: statistical table 23, volume XX, p. xx). The volume and page numbers will be inserted at the end of the project.

C. Footnotes:

Footnotes should be assigned letters, not symbols or numbers, which can be confused with the data.

D. Orientation:

Portrait tables are always preferable to landscape tables.

E. Order of data presentation:

In multiple tables with similar data, present data in the same order as much as possible. If the first column always has the active drug and the second column has the placebo or comparative agent, then keep this order throughout the tables.

F. Present meaningful data together:

Try to present the data that will be evaluated and compared as close together as possible rather than scattered around the table. For e.g., if tabular data represent both evaluable and non-evaluable patients who have been either previously treated or previously untreated, place the evaluable patient together rather than present them by previous treatment. Upon receipt of an NDA, the FDA conducts a review of the application to determine its completeness. Within 60 days, the FDA either accepts the filing or sends the applicant a "refusal-to-file" letter. If the applicant receives a "refusal-to-file" letter, they can request a conference with FDA.

Grounds for refusal to file the application include:

1. Form FDA 356h has not been completed.
2. The format of the application is not correct.
3. One or more item is missing from the content as described in the regulations.
4. The manufacturing facilities are not ready for inspection.
5. Complete and accurate translations of all parts of the application not in English are notincluded.
6. There are no statements regarding GLP compliance for each of the non clinical studies.
7. There are no statements regarding compliance with IRB and informed consent regulations foreach of the clinical studies.
8. The drug product is already covered by an approved NDA or ANDA.

At this stage FDA will send one of three possible action letters to the applicant:

One possibility is a "Not Approvable Letter," which will list the deficiencies in the NDA and explain why it cannot be approved. The second possibility is an "Approvable Letter," which indicates that ultimately the drug product should be approved, but lists minor deficiencies and labeling changes that are needed before an approval. Requests for commitment for post-approval studies may be included. The third possibility is an "Approval Letter," it states that the drug is approved. An applicant may receive both an Approvable Letter and Approval Letter. Division director of CDER, signs and approve a letter that the product can be legally marketed, starting on that date onwards.

Updates [9, 10]

FDA approves first implantable hearing device for adults with a certain kind of hearing loss. The U.S. Food and Drug Administration approved the first implantable device for people 18 and older with severe or profound sensor neural hearing loss of high-frequency sounds in both ears, but who can still hear low-frequency sounds with or without a hearing aid. The Nucleus Hybrid L24 Cochlear Implant, System may help those with this specific kind of hearing loss who do not benefit from conventional hearing aids.

Source: FDA News Release, Date 21/3/2014

CONCLUSION

This article provides the valuable information about the types and its classification, The NDA provides enough information to permit FDA reviewer to reach safety, efficacy and quality for pharmaceutical production. Now a day, regulatory guidelines are most important to assess and development for consideration. The international treaties are very important for regulation. The Component for drug approval process which required submits to USFDA before drug

commercialization. The Data gathered during the animal studies and human clinical trials of an Investigational New Drug (IND) become part of the NDA.

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