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DOCUMENTS REQUIRED FOR NEW DRUG APPLICATION (NDA) : A REVIEW

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ABSTRACT

A regulatory process by which a person/organization/sponsor/innovator gets authorization to launch a drug in the market, is known as drug approval process. In general, a drug approval process comprises of various stages, application to conduct clinical trials, conducting clinical trials, application to marketing authorization of drug and post-marketing studies. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs. The purpose of this article is to present a concise Overview of the drug approval process. It will briefly review the history of the FDA and follow the journey of a new product from early development until approval by the FDA for prescription use.

Key words: NDA, Clinical trial, FDA

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INTRODUCTION

What is a New Drug Application (NDA)?

The NDA is the vehicle through which drug sponsors (pharma companies) formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S. The data gathered during the animal studies and human clinical trials of an Investigational New Drug (IND) become part of the NDA.

In simple terms "It is an application filed with USFDA to get approval for marketing a new pharmaceutical for sale in the U.S." Since 1938, every new drug has been the subject of an approved NDA before U.S. commercialization.

Goals of NDA

The goals of the NDA are to provide enough information to permit FDA reviewer to reach the following key decisions:

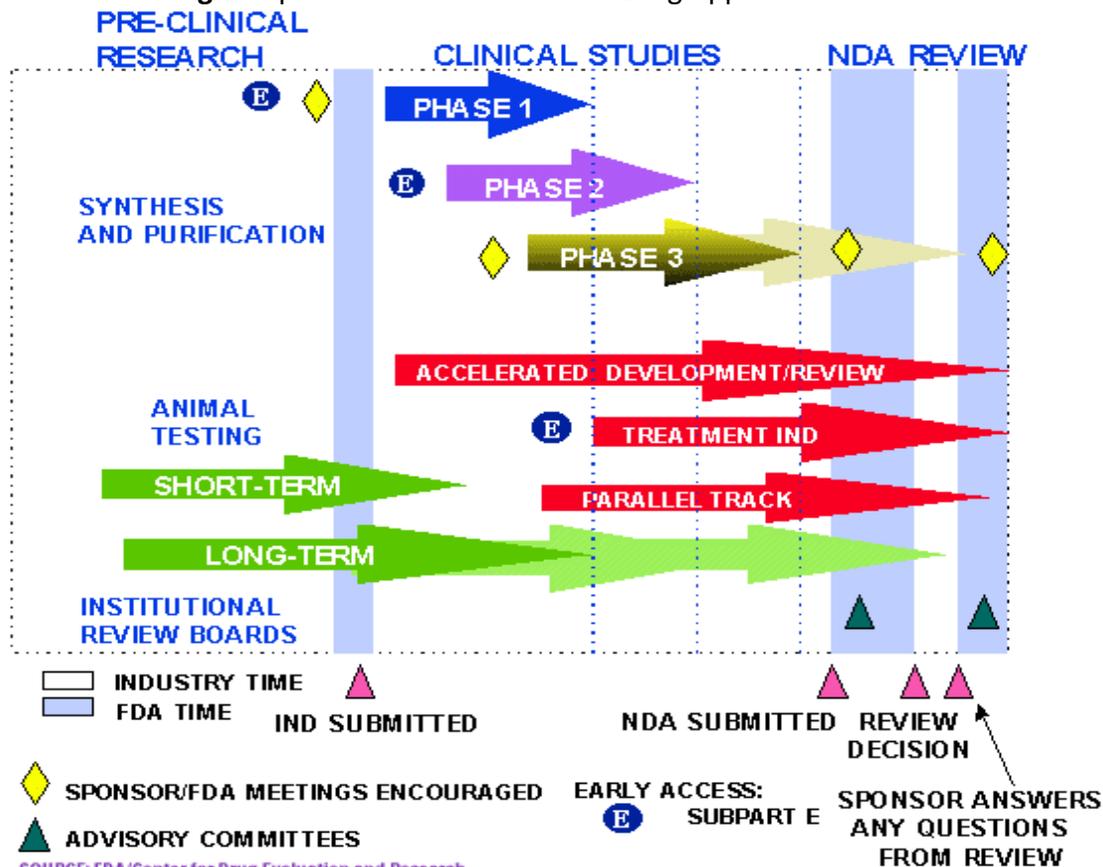
- Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.
- Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain.
- Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.^[1]

Drug Development

Drug development can generally be divided into phases. The first is the preclinical phase, which usually takes 3 to 4 years to complete. If successful, this phase is followed by an application to the FDA as an investigational newdrug (IND). After an IND is approved, the next steps are clinical phases 1, 2, and 3, which require approximately 1, 2, and 3 years, respectively. Importantly, throughout this process the FDA and investigators leading the trials communicate with each other so that such issues

as safety are monitored. The manufacturer then files a newdrug application (NDA) with the FDA for approval. This application can either be approved or rejected, or the FDA might request further study before making a decision. Following acceptance, the FDA can also request that the manufacturer conduct additional postmarketing studies. Overall, this entire process, on average, takes between 8 to 12 years.^[2] Figure 1 summarizes the drug approval process.

Fig.1 Steps from Test Tube to New Drug Application Review



SOURCE: FDA/Center for Drug Evaluation and Research

It is not surprising that from conception to market most compounds face an uphill battle to become an approved drug. For approximately every 5,000 to 10,000 compounds that enter preclinical testing, only one is approved for marketing.^[3] A 1993 report by the Congressional Office of Technology Assessment estimated the cost of developing a new drug to be \$359 million.^[4] Newer figures place the cost at more than \$500 million.^[5] The first step, a preclinical phase, is to find a promising agent, which involves taking

advantage of the advances made in understanding a disease, pharmacology, computer science, and chemistry. Breaking down a disease process into its components can provide clues for targeting drug development. For example, if an enzyme is determined to be a key component of a disease process, a researcher might seek ways to inhibit this enzyme. The next step before attempting a clinical trial in humans is to test the drug in living animals, usually rodents. The FDA requires that certain animal tests be conducted before humans are

exposed to a new molecular entity. For example, tests should prove that the compound does not cause chromosomal damage and is not toxic at the doses that would most likely be effective. The results of these tests are used to support the IND application that is filed with the FDA. The IND application includes chemical and manufacturing data, animal test results, including pharmacology and safety data, the rationale for testing a new compound in humans, strategies for protection of human volunteers, and a plan for clinical testing.^[2,4] If the FDA is satisfied with the documentation, the stage is set for phase 1 clinical trials. Phase 1 studies focus on the safety and pharmacology of a compound.^[6] During this stage low doses of a compound are administered to a small group of healthy volunteers who are closely supervised. In cases of severe or life-threatening illnesses, volunteers with the disease may be used. Generally, 20 to 100 volunteers are enrolled in a phase 1 trial. These studies usually start with very low doses, which are gradually increased. On average, about two thirds of phase 1 compounds will found safe enough to progress to phase 2. Phase 2 studies examine the effectiveness of aCompound. Typically, phase 2 studies involve 100 to 300 patients who suffer from the condition the new drug is intended to treat. During phase 2 studies, researchers seek to determine the effective dose, the method of delivery (e.g., oral or intravenous), and the dosing interval, as well as to reconfirm product safety.^[2,6,7,8] Patients in this stage are monitored carefully and assessed continuously. A substantial number of these drug trials are discontinued during phase 2 studies. Some drugs turn out to be ineffective, while others have safety problems or intolerable side effects.

Phase 3 trials are the final step before seeking FDA approval. During phase 3, researchers try to confirm previous findings in a larger population. These studies usually last from 2 to 10 years and involve thousands of patients across multiple sites. These studies are used to demonstrate further safety and effectiveness and to determine the best dosage. Despite the intense scrutiny a product receives before undergoing

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expensive and extensive phase 3 testing, approximately 10% of medications fail in phase 3 trials. If a drug survives the clinical trials, an NDA is submitted to the FDA. An NDA contains all the preclinical and clinical information obtained during the testing phase. The application contains information on the chemical makeup and manufacturing process, pharmacology and toxicity of the compound, human pharmacokinetics, results of the clinical trials, and proposed labelling. An NDA can include experience with the medication from outside the United States as well as external studies related to the drug.^[9]

Preparation of documents for NDA^[10]

Documents represent the Agency's current thinking on a particular subject. These documents are prepared for FDA review staff and applicants/sponsors to provide guidelines to the processing, content, and evaluation/approval of applications and also to the design, production, manufacturing, and testing of regulated products.

Classification of drugs according to NDA^[11]

Type 1: new molecular entity

Type 2: new salt of previously approved drug

Type 3: new formulation of previously approved drug(not a new salt or new molecular entity)

Type 4: new combination of two or more drugs

Type 5: already marketed product-duplication (i.e.: new manufacturer)

Type 6: new indication (claim)for already marketed drug(includes switch in marketing status from prescription to OTC)

Type 7: already marketed drug product & no previously approved NDA

Fundamentals of NDA Submission^[12,13]

As outlined in Form FDA-356h, Application to Market a New Drug for Human Use Or As An Antibiotic Drug For Human Use, NDAs can consist of as many as 15 different sections:

- Index
- Summary
- Chemistry, Manufacturing, and Control;
- Samples, Method Validation Package, and Labelling
- Nonclinical Pharmacology and Toxicology

- Human Pharmacokinetics and Bioavailability
- Microbiology (for anti-microbial drugs only);
- Clinical Data;
- Safety Update Report (typically submitted 120 days after the NDA's submission);
- Statistical
- Case Report Tabulations;
- Case Report Forms;
- Patent Information;
- Patent Certification; and
- Other Information.

General Requirements

The new (present) NDA regulations require that an application be submitted in two copies:-

- (a) An archival copy:- that serves as a permanent record of the submission, it is submitted in BLUE color folder and the archival copy of the application should include a comprehensive index by volume and page number. It is recommended that additional copies of the index be prepared and included with any material submitted to FDA for the NDA.
- (b) A review copy:- The review copy is made up of a number of separate technical volumes, each tailored to the needs of the disciplines involved in the review.

Both the archival and review copies are submitted in hard copy, the regulations permit an application to submit the archival copy as microchip.

The application form is supplemented with detailed, technical guidelines to improve the quality of submissions:

- The format and content of an application summary
- Formatting, assembling and submitting new drug and antibiotic applications
- The format and content of the human Pharmacokinetics and Bioavailability section of an application
- The format and content of the clinical and statistical sections of an application.
- Submission of chemistry section earlier than 120 days and less than 90 days before the remainder of the application will not be accepted.
- The archival copy of the application should include a comprehensive index by volume and

page number. It is recommended that additional copies of the index be prepared and included with any material submitted to FDA for the NDA. This will easily access locating important parts of the submission that may be needed for meetings / view by individual technical reviewers.

1. INDEX

The archival copy of the application should include a comprehensive index by volume and page number. It is recommended that additional copies of the index be prepared and included with any material submitted to FDA for the NDA.

2. SUMMARY

It has been suggested that the summary consists of 50 - 200 pages. The summary should discuss all aspects of the application and needs to be written at approximately level of detail required for publication and meet the editorial standards applied by referred scientific and medical journals. It is advantageous to provide data in the summary in tabular and graphic form with clear explanation of any terminology used in the tabulations or graphics.

3. CHEMISTRY, MANUFACTURING AND CONTROLS

Chemistry, manufacturing and controls summary must provide a general overview of the drug substance and drug product.

- Drug substance:- Description including physical and chemical characteristics and stability
- Drug product:- Composition and type of dosage form, manufacture, specifications and analytical methods, container/closure system, stability, investigational formulations.

Details are provided in 21CFR 25.1

The chemistry section, because of its length, and highly detailed sections dealing with the manufacturing and control processes, is required to be submitted 90-120 days prior to the submission of the application for facilitating the identification of deficiencies in the filed NDA. Submission of chemistry section earlier than 120 days and less than 90 days before the remainder of the application will not be accepted.

Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Products

- ✓ Description and Composition of the Drug Product
- ✓ Pharmaceutical Development
- ✓ Manufacture
- ✓ Control of Excipients
- ✓ Control of Drug Product
- ✓ Reference Standards or Materials
- ✓ Container Closure System
- ✓ Stability

4. SUBMITTING SAMPLES AND ANALYTICAL DATA FORMETHODS VALIDATION.

- ✓ List of all proposed regulatory specification.
- ✓ Information supporting the integrity of the reference standard.
- ✓ Detailed description of each method of analysis.
- ✓ Information supporting the suitability of the methodology for new drug substance.
- ✓ Information supporting the suitability of the methodology for the dosage form.

5. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

Nonclinical laboratory studies include any in vivo/in vitro experiment with the test drug to determine its safety, activity or disposition. This section includes Toxicological effects of drugs on reproduction and the developing foetus, ADME animal experiments of the drugs. This section should provide a description, tabulation and graphics from Nonclinical laboratory studies of drug.

Format and Content of the Nonclinical Pharmacology/Toxicology Section of an Application

- Table of contents & cross references
- Summary discussion
- Order of presentation of studies
- Format & content of individual studies
 - Pharmacological studies
 - Acute toxicity studies
 - Sub chronic or chronic carcinogenicity studies
 - Special toxicity studies

- Reproduction studies
- Mutagenicity studies
- ADME studies
- Multi dose toxicity studies
- Format for carcinogenicity study data

6. HUMAN PHARMACOKINETICS AND BIOAVAILABILITY

- First section: There should be an overall tabulated summary of all in vivo biopharmaceutic studies carried out on the drug grouped by type of study.
- Second section: The summary of bioavailability or pharmacokinetic data and overall conclusions (C_{max}, T_{max}, K_{el}, AUC etc.)
- Third section: List of all formulations used in clinical trials and in vivo bioavailability or pharmacokinetic studies together with each formulation used in studies.
- Fourth section: Analytical methods used to measure the levels of drug and major metabolite
- Fifth section: Dissolution data on each strength and dosage form for which approval is being sought. A comparative dissolution study with the lot(s) used. In vivo biopharmaceutics studies should also be included.

7. MICROBIOLOGY

Applicable to anti-infective and antiviral drugs. It should include description of:-

- Biochemical basis of the drug's action / microbial physiology.
- Antimicrobial spectra of the drug, including results of invitro preclinical studies that demonstrate effectiveness.
- Any known mechanisms of resistance to the drug, including results of epidemiological studies to demonstrate prevalence of resistance factors.
- Clinical microbiological laboratory methods needed for effective use of the drug.
- Pharmacokinetics
- Enzyme hydrolysis rates.
- Miscellaneous studies
- Assessment of resistance
- Clinical lab susceptibility test methods
- In-vivo animal protection studies

- In-vitro studies conducted during clinical trial
- Conclusions
- Published literature

8. CLINICAL DATA

This section includes descriptions, summaries and analysis of:

- Clinical pharmacology studies including animal study and toxicology.
- Controlled clinical studies including the protocol and description of the statistical analysis used to evaluate the studies.
- Uncontrolled clinical studies, including all necessary details of the studies.
- Any other data/information relevant to an evaluation of safety and effectiveness obtained from any source, foreign or domestic (U.S.).

9. STATISTICS

This includes description and documentation of the statistical analyses performed to evaluate the controlled clinical trials and other safety information. It must include copies of:

- All controlled clinical trial reports.
- Integrated efficacy and safety summaries.
- Integrated summary of risks and benefits.

10. SAFETY UPDATE REPORTS

In 21 CFR 314.50 (d) (5) (vi) (b), the FDA details the necessity to periodically update a pending application with new safety information which affects the statements of contraindications, warnings, precautions and adverse reactions in the draft labeling. The safety update reports are required to include the same kinds of information from clinical or animal studies as well as other sources, and must be submitted in the same format as the previously described integrated summary of safety. These safety reports must be submitted as follows:

- Four months after the initial submission
- Following receipt of an approvable letter
- At other times as requested by FDA

In case of any adverse drug experience, the surveillance system requires the reporting of such experience as soon as possible within 15 working days of initial receipt of the information. These 'alert reports' are required to be submitted on

Form FDA 1639 (Drug Experience Report). All reactions subject to 15 day alert report require follow-up reports within 15 working days of receipt of new information

11. CASE REPORT FORM TABULATION

It include complete tabulation for each patient from every adequately well controlled phase 2 and phase 3 efficacy study a form every phase 1 clinical pharmacology study. It also includes tabulation of safety data from all clinical studies

12. CASE REPORT FORMS (CRFS)

It is necessary to include the complete CRF for each patient who died during a clinical study and any patients who weredropped from the study due to an adverse effect regardless of whether the adverse effect is considered to be related to study drug even if the patient was receiving a comparative drug. Additional CRFs must be provided at request of the FDA.

NDA REGULATIONS^[12]

Review Time Frames (21 CFR 314.100) This time frames includes:

- Within 180 days of receipt of an application, the FDA will review and issue an approval, approvable, or not approvable letter. This 180-day period is called the 'review-clock'
- During the review period an applicant may withdraw an application (21 CFR 314-65) and later resubmit it.
- The time period may be extended by mutual agreement between the FDA and the applicant or as the result of submission of a major amendment (21 CFR 314.60)

Filing Time Frames (21 CFR 314.101):

- Within 60 days after the FDA receives an application, a determination will be made whether the application may be filed.
- This will determine whether sufficient information is provided to proceed with an in-depth review of application.
- If FDA files the application, the applicant will be notified in written. The date of filing will be the date 60 days after the FDA received the application.

- The date of filing begins the 180-days period of the review. If FDA refuses to file the application, the sponsor will be given the opportunity to meet with FDA to discuss the reasons why the application is not fileable.

CONCLUSION

Generally, the drug approval process comprised mainly the two steps, application to conduct clinical trial and application to the regulatory authority for marketing authorization of drug. The new drug approval process of various countries is similar in some of the aspects whereas it differs in some aspects. The sponsor firstly files an application to conduct clinical trial, and only after the approval by the regulatory authority, the applicant conducts the clinical studies and further submits an application to the regulatory authority for marketing authorization of drug. For the purpose of harmonisation, the International Conference on Harmonisation (ICH) has taken major steps for recommendations in the uniform interpretation and application of technical guidelines and requirements.

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