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Review

Comparative Study Of New Drug Application Procedure In Us, Eu And India

B. Shivasai*[1], Shaik Zareena Begum[1], S. Sunayana[1]

Department Of Regulatory Affairs, Princeton College Of Pharmacy, Narapally, Ghatkesar, Telangana, India

*Author for Correspondence: B. Shivasai
Email: pcopaac2007@gmail.com

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Abstract

Developing a new drug requires great amount of research work in chemistry, manufacturing, controls, preclinical science and clinical trials. Drug reviewers in regulatory agencies around the world bear the responsibility of evaluating whether the research data support the safety, effectiveness and quality control of a new drug product to serve the public health. 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. This article focuses on drug approval process in different countries like USA, Europe and India.

Keywords: MAA USFDA Drug approval Clinical trial.

INTRODUCTION

For decades, the regulation and control of new drugs in the United States has been based on the New Drug Application (NDA). Since 1938, every new drug has been the subject of an approved NDA before U.S. commercialization. The NDA application is the vehicle through which drug sponsors 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.

New Drug Application (NDA)

The Food and Drug Administration's new drug application (NDA) is the vehicle in the United States through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing. 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.

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 are, the results of the animal studies, how the drug behaves in the body, and how it is manufactured, processed and packaged[1].

FDA Drug Review and Approval Time

FDA is often asked about the pace of drug approvals and how FDA review time for applicationsaffects it. Since the Prescription Drug User Fee Act (PDUFA) was passed in 1992, FDA has metand often exceeded the vast majority of review-time goals established under the Act. New drugapproval times also have been dramatically reduced (from a median of 22 months in 1992 to amedian of less than 12 months in 1999), although a slight increase was seen for the year 2000.

Definitions

FDA Review Time: The time it takes FDA to review a new drug application. Review time goalsare established under PDUFA.

Approval Time: Approval time is the time from first NDA submission to NDA approval. Itincludes the sum of: FDA review time for the first submission of an NDA to the Agency, plusany subsequent time during which a pharmaceutical sponsor addresses deficiencies in the NDAand resubmits the application, plus subsequent FDA review time.

New Molecular Entity (NME): A medication containing an active substance that has neverbefore been approved for marketing in any form in the United States.

Priority New Drug Application (NDA): An application for a product determined to provide a significant therapeutic or public health advance. Priority NDAs have a 6-month FDA reviewperformance goal.

The following resources provide summaries on NDA content, format, and classification, plus the NDA review process:

Resources for NDA Submissions[1]

The following resources have been gathered to provide you with the legal requirements of a new drug application, assistance from CDER to help you meet those requirements, and internal NDA review principles, policies and procedures.

Guidance Documents for NDAs

Guidance 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. They also establish policies intended to achieve consistency in the Agency's regulatory approach and establish inspection and enforcement procedures. Because guidances are not regulations or laws, they are not enforceable, either through administrative actions or through the courts. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Guidance documents to help prepare NDAs include:

Laws, Regulations, Policies and Procedures

The mission of FDA is to enforce laws enacted by the U.S. Congress and regulations established by the Agency to protect the consumer's health, safety, and pocketbook. The Federal Food, Drug, and Cosmetic Act is the basic food and drug law of the U.S. With numerous amendments, it is the most extensive law of its kind in the world. The law is intended to assure consumers that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging is truthful, informative, and not deceptive.

Code Of Federal Regulations (CFR)

The final regulations published in the Federal Register (daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the CFR. The CFR is divided into 50 titles which represent broad areas subject to Federal regulations. The FDA's portion of the CFR interprets the Federal Food, Drug and Cosmetic Act and related statutes. Section 21 of the CFR contains all regulations pertaining to food and drugs. The regulations document all actions of all drug sponsors that are required under Federal law.

- 21CFR Part 314 - Applications for FDA Approval to Market a New Drug or an Antibiotic Drug.

e) CDER's Manual of Policies and Procedures (MaPPs)

These documents are approved instructions for internal practices and procedures followed by CDER staff to help standardize the new drug review process and other activities. MaPPs define external activities as well. All MaPPs are available for the public to review to get a better understanding of office policies, definitions, staff responsibilities and procedures. MaPPS of particular interest to NDA applicants include:

- 5015-6 Review of the Same Supplemental Change to More than One NDA or ANDA in More Than One Review Division (Issued 1/14/2000, Posted 1/19/2000)
- 6010.5 NDAs: Filing Review Issues (Issued 5/8/2003, Posted 5/14/2003)
- 6020.8 Action Packages for NDAs and Efficacy Supplements (Issued 11/13/2002, Posted 12/11/2002)
- 6050.1. Refusal to Accept Application for Filing From Applicants in Arrears
- 7211.1. Drug Application Approval 501(b) Policy
- 7600.6. Requesting and Accepting Non-Archivable Electronic Records for New Drug Applications.

Prescription Drug User Fee Act (PDUFA)

On November 21, 1997, The President signed the Food and Drug Administration Modernization Act of 1997. This legislation includes authorization for FDA to continue to collect three types of user fees from applicants who submit certain new drug and biologicalproduct applications. FDA was first authorized to collect user fees under the Prescription Drug User Fee Act (PDUFA) of 1992.

- Prescription Drug User Fee Act Related Documents

NDA Forms and Electronic Submissions

- Form FDA-356h. Application to Market a New Drug, Biologic, or An Antibiotic Drug For Human Use
- Form FDA-356h instructions
- Form FDA-3397. User Fee Cover Sheet
- Form FDA-3331. New Drug Application Field Report
- Guidance Documents for Electronic Submissions
- For more information on electronic submissions, see ERSR

Advisory Committees

Advisory committees provide independent advice and recommendations to the FDA on scientific and technical matters related to the development and evaluation of products regulated by the Agency. CDER requests advice from advisory committees on a variety of matters, including various aspects of clinical investigations and applications for marketing approval of drug products. Committee members are scientific experts such as physician-researchers and statisticians, as well as representatives of the public, including patients. Although the committees provide recommendations to the Agency, final decisions are made by FDA.

- FDA Advisory Committees
- CDER Advisory Committees
- CFR 21 Part 14 Public Hearing Before a Public Advisory Committee. Detailed description of advisory committees from the Code of Federal Regulations.
- Guidance for Industry: Advisory Committees. Includes information on membership, conflict of interest, scheduling, and action on recommendations.
- List of Tentative Meeting Dates for Advisors and Consultants Staff. Several dates have been set aside by CDER advisory committees for possible future meetings
- The subject matter and location of the meetings (if they are held) will be published in the Federal Register in the month prior to the meeting date.
- FDA Meeting Transcripts 1995 to Present. Recent transcripts includes minutes, briefing information, slides and other documents.

Before trials[2]

To legally test the drug on human subjects in the U.S., the maker must first obtain an Investigational New Drug (IND) designation from FDA. This application is based on nonclinical data, typically from a combination of in vivo and in vitro laboratory safety studies, that shows the drug is safe enough to test in humans.

Often the "new" drugs that are submitted for approval include new molecular entities or old medications that have been chemically modified to elicit differential pharmacological effects or reduced side-effects.

Clinical trials

The legal requirement for approval is "substantial" evidence of effectiveness demonstrated through controlled clinical trials This standard lies at the heart of the regulatory program for drugs. It means that the clinical

experience of doctors, the opinion of experts, or testimonials from patients, even if they have experienced a miraculous recovery, have minimal weight in this process. Data for the submission must come from rigorous clinical trials.

The trials are typically conducted in three phases:

- Phase 1: The drug is tested in a few healthy volunteers to determine if it is acutely toxic.
- Phase 2: The drug is tested for both efficacy and safety in a larger sample pool. The majority of drugs fail in Phase 2 clinical trials due to the drug not being as effective as anticipated.
- Phase 3: The drug is typically tested in double-blind, placebo controlled trials to demonstrate that it works. Sponsors typically confer with FDA prior to starting these trials to determine what data is needed, since these trials often involve hundreds of patients and are very expensive.
- (Phase 4): These are post-approval trials that are sometimes a condition attached by the FDA to the approval.

The actual application

The results of the testing program are codified in an FDA-approved public document that is called the product label, package insert or Full Prescribing Information. The prescribing information is widely available on the web, from the FDA, drug manufacturers, and frequently inserted into drug packages. The main purpose of a drug label is to provide healthcare providers with adequate information and directions for the safe use of the drug.

Requirements for similar products

Biologics, such as vaccines and many recombinant proteins used in medical treatments are generally approved by FDA via a Biologic License Application (BLA), rather than an NDA. The manufacture of biologics is considered to differ fundamentally from that of less complex chemicals, requiring a somewhat different approval process. Generic drugs that have already been approved via an NDA submitted by another maker are approved via an Abbreviated New Drug Application (ANDA), which does not require all of the clinical trials normally required for a new drug in an NDA. Most biological drugs, including a majority of recombinant proteins are considered ineligible for an ANDA under current US law. However, a handful of biologic medicines, including biosynthetic insulin, growth hormone, glucagon, calcitonin, and hyaluronidase are grandfathered under governance of the Federal Food Drug and Cosmetics Act, because these products were already approved when legislation to regulate biotechnology medicines later passed as part of the Public Health Services Act.

Breaking down 'new drug application (nda)'[3]

The NDA has formed the basis for regulating and controlling new drugs in the U.S. since 1938, and has evolved significantly since then. Under the Food, Drug and Cosmetic Act (FD&C) passed in 1938, NDAs were only required to contain information relating to the proposed new drug's safety. In 1962, amendments to the FD&C Act required NDAs to also include evidence on the new drug's effectiveness for its intended use, and confirm that its established benefits outweighed its known risks. In 1985, the FDA completed a review of NDA regulations and in order to expedite the review process, restructured the organization and presentation of information and data contained in the NDA.

Once the CDER review of an NDA is completed, it issues one of three possible action letters to the sponsor of the new drug –

- Approval Letter: this states that the drug is approved.
- Approvable Letter: indicates that the drug can be ultimately approved, but lists minor deficiencies that need to be rectified; it often asks for labeling changes and sometimes for sponsor commitment to undertake post-marketing studies.
- Not Approvable Letter – lists deficiencies in the application and the reasons why the drug cannot be approved.

Investigational New Drug (IND) Application[4]

Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer), having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans. At that point, the molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system.

There are three IND types:

- An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.
- Emergency Use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR , Sec. 312.23 or Sec. 312.34. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.
- Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

There are two IND categories:

- Commercial
- Research (non-commercial)

The IND application must contain information in three broad areas:

- Animal Pharmacology and Toxicology Studies - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experience with the drug in humans (often foreign use).
- Manufacturing Information - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.
- Clinical Protocols and Investigator Information - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators--professionals (generally physicians) who oversee the administration of the experimental compound--to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.

Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk.

Resources for IND Applications

The following resources include the legal requirements of an IND application, assistance from CDER to help you meet those requirements, and internal IND review principles, policies and procedures.

Pre-IND Consultation Program

CDER's Pre-Investigational New Drug Application (IND) Consultation Program fosters early communications between sponsors and new drug review divisions to provide guidance on the data necessary to warrant IND submission. The review divisions are organized generally along therapeutic class and can each be contacted using the designated Pre-IND Consultation List (PDF - 19KB)

Guidance Documents for INDs

Guidance documents represent the Agency's current thinking on a particular subject. These documents provide FDA review staff and applicants/sponsors with guidelines to the processing, content, and evaluation/approval of applications and also to the design, production, manufacturing, and testing of regulated products. They also establish policies intended to achieve consistency in the Agency's regulatory approach and establish inspection and enforcement procedures.

Because guidances are not regulations or laws, they are not enforceable, either through administrative actions or through the courts. An alternative approach may be used if it satisfies the requirements of the applicable statute, regulations, or both. For information on a specific guidance document, please contact the originating office.

Laws, Regulations, Policies and Procedures

The mission of FDA is to enforce laws enacted by the U.S. Congress and regulations established by the Agency to protect the consumer's health, safety, and pocketbook. The Federal Food, Drug, and Cosmetic Act is the basic food and drug law of the U.S. The law is intended to assure consumers that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging is truthful, informative, and not deceptive.

Code of Federal Regulations (CFR)

The final regulations published in the Federal Register (daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the Code Of Federal Regulations (CFR). The CFR is divided into 50 titles that represent broad areas subject to Federal regulations. The FDA's portion of the CFR interprets the The Federal Food, Drug, and Cosmetic Act and related statutes. Section 21 of the CFR contains most regulations pertaining to food and drugs. The regulations document all actions of all drug sponsors that are required under Federal law.

Manual of Policies and Procedures (MaPPs)

CDER's Manual of Policies and Procedures (MaPPs) are approved instructions for internal practices and procedures followed by CDER staff to help standardize the new drug review process and other activities. All MAPPs are available for the public to review for a better understanding of office policies, definitions, staff responsibilities and procedures. MaPPs of particular interest to IND sponsors include:

- 4200.1 Consulting the Controlled Substance Staff on INDs and Protocols That Use Schedule I Controlled Substances and Drugs (Issued 5/8/2003)
- 5210.5 Review of Investigational New Drug Applications (Bio-INDs) by the Office of Generic Drugs
- 6030.1 IND Process and Review Procedures (Including Clinical Holds). Includes general IND review principles, policies and procedures for issuing clinical holds of INDs, and processing and responding to sponsors' complete responses to clinical holds.
- 6030.2 INDs: Review of Informed Consent Documents (Issued 11/13/2002)
- 6030.4 INDs: Screening INDs. (Issued 5/9/2001, Posted 5/14/2001). This MsPP describes procedures for the review of multiple active moieties or formulations under the single investigative new drug application (IND) called a screening IND.
- 6030.8 INDs: Exception from Informed Consent Requirements for Emergency Research. (Issued 2/4/2003)

Emergency Use of an Investigational Drug or Biologic

- Final Rules for Expanded Access to Investigational Drugs for Treatment Use and Charging for Investigational Drugs (8/12/2009)
- FDA proposes rules overhaul to expand the availability of experimental drugs. The Agency also clarifies permissible charges to patients. FDA News (12/11/2006)
- The Guidance for Institutional Review Boards and Clinical Investigators contains information on: Obtaining an Emergency IND, Emergency Exemption from Prospective IRB, Approval Exception from Informed Consent, and Requirement Planned Emergency Research, Informed Consent Exception.
- Federal Register notice for Emergency Use of an Investigational New Drug; Technical Amendment
- Physician Request for a Single Patient IND for Compassionate or Emergency Use
- Instructions for Sponsors of Emergency Investigational New Drug (EIND) Applications for Antimicrobial Products. From the Office of Antimicrobial Products, Division of Antiviral Products (11/29/2005).

Abbreviated New Drug Application[5-6]

An Abbreviated New Drug Application (ANDA) is an application for a U.S. generic drug approval for an existing licensed medication or approved drug.

The ANDA is submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, which provides for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public. Electronic submissions of ANDAs have grown by 70% since November 2008. The Section IV challenge has been credited with suppressing new drug innovation.

A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use. All approved products, both innovator and generic, are listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book).

Resources for ANDA Submissions

The following resources have been gathered to provide you with the legal requirements of an ANDA application, assistance from CDER to help you meet those requirements, and internal ANDA review principles, policies and procedures.

Guidance Documents for ANDAs

Guidance 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. They also establish policies intended to achieve consistency in the Agency's regulatory approach and establish inspection and enforcement procedures. Because guidances are not regulations or laws, they are not enforceable, either through administrative actions or through the courts. An alternative approach may be used if such an approach satisfies the requirements of the applicable statute, regulations, or both. For information on a specific guidance document, please contact the originating office.

The FDA has numerous guidances that relate to ANDA content and format issues. Below is a list of some recent Guidances of interest. See Drug Information Branch's Guidance Documents for a complete list of available guidances online and instructions on how to obtain them.

Guidance documents to help prepare ANDAs are listed together on CDER's Guidance Document Index web page in the following categories:

Laws, Regulations, Policies and Procedures

The mission of FDA is to enforce laws enacted by the U.S. Congress and regulations established by the Agency to protect the consumer's health, safety, and pocketbook. The Federal Food, Drug, and Cosmetic Act is the basic food and drug law of the U.S. With numerous amendments it is the most extensive law of its kind in the world. The law is intended to assure consumers that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging is truthful, informative, and not deceptive.

Code of Federal Regulations (CFR)

Code Of Federal Regulations (CFR). The final regulations published in the Federal Register (daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the CFR. The CFR is divided into 50 titles which represent broad areas subject to Federal regulations. The FDA's portion of the CFR interprets the Federal Food, Drug and Cosmetic Act and related statutes. Section 21 of the CFR contains most of the regulations pertaining to food and drugs. The regulations document most actions of all drug sponsors that are required under Federal law. The following regulations apply to the ANDA process:

- 21CFR Part 314 Applications for FDA Approval to Market a New Drug or and Antibiotic Drug disclaimer .
- 21CFR Part 320 Bioavailability and Bioequivalence Requirements.
- 21CFR Part 310 New Drugs disclaimer

MaPPs

CDER's Manual of Policies and Procedures (MaPPs) provide official instructions for internal practices and procedures followed by CDER staff to help standardize the drug review process and other activities, both internal and external. MaPPs define external activities as well. All MAPPs are available for the public to review to get a better understanding of office policies, definitions, staff responsibilities and procedures. MaPP documents to help prepare ANDAs are listed together on CDER's Manual of Policies and Procedures webpage.

ANDA Forms and Electronic Submissions

- ANDA Filing Checklist (PDF)
- FDA Form 356h. Application to Market a New Drug for Human Use/Antibiotic Drug for Human Use
- The CDER Office of Generic Drugs has developed a guidance document entitled Providing Regulatory Submissions in Electronic Format — ANDAs (Issued 6/2002, Posted 6/27/2002) to assist applicants making regulatory submissions in electronic format of abbreviated new drug applications. This guidance should be used in conjunction with the following guidances:
    - Guidance for Industry: Providing Regulatory Submissions in Electronic Format - General Considerations.
    - Regulatory Submissions in Electronic Format; New Drug Applications.

How Drugs are Developed and Approved[7]

The mission of FDA's Center for Drug Evaluation and Research (CDER) is to ensure that drugs marketed in this country are safe and effective. CDER does not test drugs, although the Center'sOffice of Testing and Research does conduct limited research in the areas of drug quality, safety, and effectiveness**.**
CDER is the largest of FDA's six centers. It has responsibility for both prescription and nonprescription or over-the-counter (OTC) drugs. For more information on CDER activities, including performance of drug reviews, post-marketing risk assessment, and other highlights, please see About the Center for Drug Evaluation and Research. The other five FDA centers have responsibility for medical and radiological devices, food and cosmetics, biologics, veterinary drugs, and tobacco products.

From Fish to Pharmacies: A story of drug development

Osteoporosis, a crippling disease marked by a wasting away of bone mass, affects as many as 2 million American, 80 percent of them women, at an expense of $13.8 billion a year, according to the National Osteoporosis Foundation., The disease may be responsible for 5 million fractures of the hip, wrist and spine in people over 50, the foundation says, and may cause 50,000 deaths. Given the pervasiveness of osteoporosis and its cost to society, experts say it is crucial to have therapy alternatives if, for example, a patient can't tolerate estrogen, the first-line treatment.

Bringing Nonprescription Drug Products to the Market Under an OTC Monograph

OTC drugs can be brought to the market following the NDA process as described above or under an OTC monograph. Each OTC drug monograph is a kind of "recipe book" covering acceptable ingredients, doses, formulations, labeling, and, in some cases, testing parameters. OTC drug monographs are continually updated to add additional ingredients and labeling as needed. Products conforming to a monograph may be marketed without FDA pre-approval. The NDA and monograph processes can be used to introduce new ingredients into the OTC marketplace. For example, OTC drug products previously available only by prescription are first approved through the NDA process and their "switch" to OTC status is approved via the NDA process. OTC ingredients marketed overseas can be introduced into the U.S. market via a monograph under a Time and Extent Application (TEA) as described in 21 CFR 330.14. For a more thorough discussion of how OTC drug products are regulated visit FDA laws, regulations and guidances that affect small business. Information is also provided on financial assistance and incentives that are available for drug development.

CDER Small Business and Industry Assistance (CDER SBIA)

Drug sponsors which qualify as small businesses can take advantage of special offices and programs designed to help meet their unique needs. The CDER Small Business and Industry Assistance (CDER SBIA) Webpage provides links to FDA laws, regulations and guidances that affect small business. Information is also provided on financial assistance and incentives that are available for drug development.

Review and approval procedures for drug submissions

Each jurisdiction has its own procedures to review drug submissions filed to their regulatory agency. These procedures can vary substantially with respect to how the drug submission will be handled, the composition of the review team, review timelines and so on.
Despite the differences, the procedures to reach regulatory approval generally follow these stages:

Pre-Submission Meeting

Although optional, a pre-submission meeting is often useful so that any scientific or submission issues can be discussed and resolved prior to the actual submission. This meeting also provides the agency insight into your drug or biologic submission and allows them to organize their internal resources accordingly.

Pre-Submission Activities

Review what communication is required prior to submitting your marketing application. In Canada, sponsors (that is, applicants) are requested to send advance requests for Priority Review status and for Requests for Advance Consideration under the NOC/c. In the EU, an applicant should notify the European Medicines Agency (EMA) of its intention to submit via the centralized procedure at least seven months before the drug submission. Any orphan drug designation should also be requested and approved before your drug submission will be reviewed as an orphan product.

Administrative review

Once a drug submission is filed, it goes through an administrative review to ensure its acceptability (for example, completeness). A submission number (such as NDS Control Number or NDA number) is assigned and this number must be used in all subsequent communication with the regulatory agency.

If the drug submission is found to be acceptable at this stage, it will be accepted for review. If minor deficiencies are identified (for example, missing forms), the agency will normally allow the sponsor time to respond. If the response is satisfactory, then the submission will proceed to review. If the sponsor fails to provide the requested information within the set timeframe, or if that the response is unsatisfactory, the agency can reject (refuse to file) the submission.

Agency review and sponsor response

Once a drug submission is accepted, it is evaluated by reviewers with the necessary expertise. In the US, for example, a review team may include clinicians, pharmacokineticists, pharmacologists, toxicologists, statisticians, microbiologists and chemists, as well as a regulatory project manager (RPM). The objective of the review is to confirm and validate the sponsor's conclusion that the drug is safe and effective for its proposed use. Once the technical review is complete, an evaluation report will be generated. If the submission is deemed acceptable, then the technical review of the submission is complete. If deficiencies are identified, then the agency will issue a list of questions for the sponsor to address within a set timeline.

This review also evaluates the text in the proposed labelling, which needs to be justified by the data submitted in the submission. If the reviewers question the proposed labelling, they will discuss revised wording with the sponsor[7].

Activities Prior To The Agency's Decision

These may include any necessarypre-approval inspections (for example, of drug manufacturing sites or clinical trial sites). In the US, for example, the Food and Drug Administration (FDA) may decide to convene an advisory committee (AC) meeting and seek input. Based on the discussions at the AC meeting and its recommendations, the FDA may ask for additional data or analyses to review.

Decision

The decision made at the end of the review process normally results in regulatory approval, an approval with conditions, or a rejection.

*NOC/c = Notice of Compliance with conditions

DISCUSSION

The Drug Approval Process[14]

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 new drug (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, for completion (Table). 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 new drug 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.Figure 6 summarizes the drug approval process.

Overview of drug development process and review. IND - investigational new drug, NDA - new drug application. Adapted from: The Drug Development Approval Process. 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. A 1993 report by the Congressional Office of Technology Assessment estimated the cost of developing a new drug to be $359 million.Newer figures place the cost at more than $500 million.

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. Advances in basic science might help by ascertaining the active enzyme site. Numerous compounds might be synthesized and tested before a promising agent emerges. Computer modeling often helps select what compounds might be the most promising.

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. The objectives of early in vivo testing are to demonstrate the safety of the proposed medication. 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. 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. 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 be found safe enough to progress to phase 2.

Phase 2 studies examine the effectiveness of a compound. To avoid unnecessarily exposing a human volunteer to a potentially harmful substance, studies are based on an analysis of the fewest volunteers needed to provide sufficient statistical power to determine efficacy. 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 (eg, oral or intravenous), and the dosing interval, as well as to reconfirm product safety. 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 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 labeling. An NDA can include experience with the medication from outside the United States as well as external studies related to the drug.

After receiving an NDA, the FDA completes an independent review and makes its recommendations. The Prescription Drug User Fee Act of 1992 (PDUFA) was designed to help shorten the review time. This act allowed the agency to collect user fees from pharmaceutical companies as financial support to enhance the review process. The 1992 act specifies that the FDA reviews a standard drug application within 12 months and a priority application within 6 months. Application for drugs similar to those on the market are considered standard, whereas priority applications represent drugs offering important advances in addition to existing treatments. If during the review the FDA staff feels there is a need for additional information or corrections, they will make a written request to the applicant. During the review process it is not unusual for the FDA to interact with the applicant staff.

Once the review is complete, the NDA might be approved or rejected. If the drug is not approved, the applicant is given the reasons why and what information could be provided to make the application acceptable. Sometimes the FDA makes a tentative approval recommendation, requesting that a minor deficiency or labeling issue be corrected before final approval. Once a drug is approved, it can be marketed.

Some approvals contain conditions that must be met after initial marketing, such as conducting additional clinical studies. For example, the FDA might request a post marketing, or phase 4, study to examine the risks and benefits of the new drug in a different population or to conduct special monitoring in a high-risk population. Alternatively, a phase 4 study might be initiated by the sponsor to assess such issues as the longer term effects of drug exposure, to optimize the dose for marketing, to evaluate the effects in pediatric patients, or to examine the effectiveness of the drug for additional indications. Post marketing surveillance is important, because even the most well-designed phase 3 studies might not uncover every problem that could become apparent once a product is widely used. Furthermore, the new product might be more widely used by groups that might not have been well studied in the clinical trials, such as elderly patients. A crucial element in this process is that physicians report any untoward complications. The FDA has set up a medical reporting program called Medwatch to track serious adverse events (1-800-FDA-1088). The manufacturer must report adverse drug reactions at quarterly intervals for the first 3 years after approval, including a special report for any serious and unexpected adverse reactions.

CONCLUSION

Any medicinal agent to be marketed in the United Kingdom has to follow the guidelines and regulations framed by MHRA, a regulatory authority which approves the drug products. The objective of this review article is to highlight information regarding the requirements, the different types of submissions for

the registration of a medicinal product in a market in the UK. It alsoincludes all the details about the fee for the application and the time period for the approval of the application after the submission of the application. By knowing the requirements of the MHRA guidelines and regulations, it is easy for a product to get into the UK market. The Drug approvals in the US, Europe & India are the most demanding in the world. The primary purpose of the rules governing medicinal products in US, Europe & India is to safeguard public health. It is the role of public regulatory authorities to ensure that pharmaceutical companies comply with regulations. There are legislations that require drugs to be developed, tested, trailed, and manufactured in accordance to the guidelines so that they are safe and patient's well – being is protected.

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