



Understanding Drug Development: A Primer on the Food and Drug Administration

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Over the past year, the Severe Acute Respiratory Syndrome Coronavirus 2 pandemic has led to rapid advancement regarding therapeutics, vaccines, and testing. In the United States, the Food and Drug Administration (FDA) is the agency ensuring standardization, reproducibility, and meeting benchmarks of safety and efficacy for these products. Among medical professionals and the public, there are often questions about the role of regulation, product development and approval, and terminology often used in regard to the FDA. This manuscript will serve as an introduction to the FDA, clarify the steps of drug development and approval, review terms related to product use, and discuss the role of the medical community and industry.

Key words. drug development; EUA; FDA; regulation.

Over the past year, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic has led to rapid advancement regarding therapeutics, vaccines, and testing. While some of these developments are based on currently used technology, others are novel approaches altogether. Although the sharing of data and transparency of products has improved over time, there is still a necessity for ensuring standardization, reproducibility, and meeting benchmarks of safety and efficacy. In the United States, this role is met through the Food and Drug Administration (FDA). There are multiple branches within the FDA, with 3 especially pertinent to infectious diseases providers. The Center for Drug Evaluation and Research (CDER) focuses on non-biologic drugs, which regarding infectious diseases are antibiotics, antifungal, and antiviral agents. The Center for Biologics Evaluation and Research (CBER) focuses on biologic-based products, such as vaccines and antibody-based products. The Center for Devices and Radiological Health (CDRH) focuses on medical testing materials and devices as well as drug product delivery mechanisms. Though there are differences in base terminology, the product approval process is similar for these branches. The author served as a medical officer in the Office of Infectious Diseases within CDER for 3 years, prior to his current role as a clinician educator. Among medical professionals and the public alike, there are often assumptions and questions about the role of regulation, product development

and approval, and terminology often used in regard to the FDA. This manuscript will serve as an introduction to the FDA, clarify the nuances of product development and approval, and discuss the role of the medical community and industry.

The FDA serves as a regulatory agency providing general guidance in product development and ensuring safety, efficacy, and quality are met in approval of drugs, vaccines, biologics, and testing products. The organization does not in its own right drive development or serve to unduly influence creation, promotion, or distribution of products [1]. Advice and oversight for each product are based on intended indication and performed studies, not necessarily what might be clinical practice. FDA approval is based solely on its own review and interactions with the developer, regardless of approval in other nations. Until the second half of the 20th century, there was little standardization or oversight of the contents, prescribing, or use of medications in the United States. Medical products could vary in formulation, dose, and delivery and potentially be more hazardous than the ailment being treated. The regulatory review process ensures that certain standards of efficacy and safety are met for all prescription medical products sold and used in the United States [2].

REGULATORY DESIGNATIONS

In order to promote efficiency in the drug approval process, adjustments and standardization of the current process started in 1992 with a joint agreement between FDA, Pharmaceutical Industry, and Congress with the Prescription Drug User Fee Act (PDUFA). It was last updated in 2017. The act results in industry sponsors paying user fees at the initiation of applications for the drug approval process and, in turn, has allowed the FDA to appropriately staff and streamline the review process [3]. PDUFA establishes a 2-tier process. There is a standard

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review, with a 10-month goal for review, which applies to products that are similar or propose only modest improvement to existing marketed products. For example, a cephalosporin, like ceftaroline fosamil, being reviewed for the indication of complicated skin and skin structure infection or community-acquired pneumonia would be given standard review. A priority review is given a 6-month goal and applies to products that fill a void or be a significant advancement from existing marketed products; baloxavir fits this designation in 2018 as a potential significant addition in anti-influenza products. In addition to priority review, there are other drug development designations meant to encourage the development of products which will have considerable benefit when compared with current drugs and ensure that the products can be available to patients as soon as the review team signifies that benefit outweighs risks [1]. Fast Track is a designation that can help advance review and discussions on a product, which must be requested by the pharmaceutical company, and given if criteria are met to show that the product will fit an unmet need for a serious or life-threatening condition. Remdesivir is a product that was given both priority review and a Fast Track designation in the treatment of Covid-19. Similarly, a product can be chosen as a Breakthrough Therapy, if initially clinical studies show a significant benefit or improvement in comparison to current therapies and, therefore, facilitate the development and review process. Artesunate for malaria, Ser-109 for *Clostridium difficile*, and Inmazeb for Ebola are some recent examples that fit this designation. Both designations are not mutually exclusive and can be placed on drugs that indicate substantial promise. In addition to these designations is the Accelerated Approvals process, which stemmed from the HIV crisis. The process was established to allow the approval and distribution of drugs indicated for serious and life-threatening illnesses which otherwise lacked adequate alternatives. New drug applications (NDAs) can be approved prior to full establishment of efficacy, if instead surrogate endpoints or targets are met, which can be labs or some clinical indications of benefit though not an exact measure of patient outcome. Some commonly used surrogate endpoints are the clearance of bacteria from blood stream as measured by lab measurement of bacteria can be a predictor of infection resolution; or clear sputum cultures and improved clinical status at 6 months predict resolution of pulmonary TB; or short-term viral suppression of HIV can be a predictor of long-term suppression. Updates are then made from post-marketing reports [4]. This allows products to potentially give benefit, even if in retrospect the promise is not maintained longitudinally.

STAGES OF CLINICAL DEVELOPMENT

On average, the process for a safe and effective product to be made and approved can take eight-and-a-half years (Table 1). Approval for pediatrics may lag years, until proper

pharmacokinetics (PK), safety, and efficacy trials are performed to allow comparative response or adequate modeled response similar to adults. The process for a drug/vaccine starts with Research and Development and Preclinical animal testing. Most of the drugs will not progress from this stage or early study phases, as drugs and vaccines must show that they are stable compounds, properly absorbed, delivered to target site, and function for noted indication, while showing positive benefit-risk profile [5].

Sponsors may consult the FDA through a pre-investigational new drug (IND) to decide if there is safe and sufficient basis to proceed to human trials. The next step is for sponsors to compile their preclinical safety efficacy, and pharmacokinetic data and modeling with proposed indication of use and proposal for human clinical trials in an IND application. The application allows the drug to be recognized as a potential therapeutic and allow transport across states and institutions. An Institutional Review Board (IRB) review occurs for each protocol and investigator, prior to the start of each study. The FDA's role in this stage is to review the IND separate from IRB approval and ensure that there is not undue harm or risks to subject, to verify there are informed consent and protection to subjects and advise sponsors to establish proper scale and focus of endpoints for studies. FDA review of an application is within 30 days of reception.

INVESTIGATIONAL NEW DRUG

An IND application does not guarantee that there will be a NDA. Phase 1 studies typically will include 20–80 healthy volunteers to determine baseline safety and pharmacokinetics. If phase 1 trials indicate no significant toxicity or safety concerns, then sponsors will start the proposed phase 2 studies primarily looking at efficacy and dosing ranges in the target population for indication. Safety is continued to be looked at as a secondary endpoint in addition to comparison to placebo or standard of care regimen. Phase 2 studies tend to have a few dozen to a few hundred participants if possible. If phase 2 trials show signs of efficacy and safety, then the sponsor will discuss and establish the benchmarks and size needed for phase 3 trials with a broad focus on clinical efficacy and safety and finalizing dosing. These studies have hundreds to thousands of participants depending on the type of product, the endpoints to be reached, and the ability to extrapolate and model the data collected [3, 6].

NEW DRUG APPLICATION

At the conclusion of phase 3 trials, a pre-NDA meeting may occur between the sponsor and FDA, to determine if there are adequate trial data to support review and approval of the proposed indications and the format and content of the NDA. Submission of a NDA is then the next aspect, which is the

official step of asking the FDA to consider the drug for approval. A Biological License Application (BLA) is similar to an NDA but with focus on biologics and vaccines. Once an NDA is received, the FDA must decide on filing for review within 60 days. Concerns with the NDA filing are sent back to the sponsor for correspondence. If filed, the FDA assigns an official review team of FDA employees consisting of physicians, pharmacists, scientists, statisticians, and other staff, which reviews for the specific product indications such as the safety, efficacy, and pharmacokinetics and verifies statistical data associated with the product. This also includes preclinical studies, assay and standard verification, clinical trial data, proposed, labeling, safety updates, patient information, IRB compliance data, directions for use, and any international data on the product. The product label that will be supplied with the product is reviewed and critiqued by the FDA team as well. In addition, the FDA will send inspectors to the manufacturer's facilities to ensure that cleanliness and quality of product are meet standards and ability to scale up for distribution. The FDA team will compile their reviews, final label edits, and facility inspection findings and will then approve the application for marketing or issue a response letter to address issues or concerns that would need to be met prior to approval. The time frame to complete the review, labeling comments, and inspections is based on the designation of Standard or Priority review [3, 7]. Of note, the decision to take a product to market after approval is the decision of the sponsor.

OFF-LABEL USE

Products may still be used even if full approval for an indication is not established. The most common aspect is off-label use. As noted, products are regulated and given approval for specific indications, dosages, ages, and weights based on the submitted materials from a sponsor. Use of a drug varying from any of these specifications outlined in the product label is considered off-label use. The FDA does not directly restrict this type of use, leaving the medical necessity as well as weighing of risks and benefits in the medical providers' authority [8]. This can be helpful particularly in the use of products for children, who are often not included in initial drug indications. However, given that the use of a drug off-label can carry harm or may not be translatable beyond individual cases, it is forbidden by law for pharmaceutical agencies to promote these off-label uses until safety and efficacy for the new indication can be proven, although, by means of the FDA Modernization Act, manufacturers can provide providers with published literature on off-label uses for purposes of current or future studies [9].

PEDIATRIC PRODUCTS

Off-label use is common in the pediatric population. Prior to 2003, less than 22% of drug labels had pediatric indications;

however, due to key legislation with a focus on improving the speed and number of products available, the percent increased to 46% by 2009. The Pediatric Research Equity Act (PREA) from 2003 requires the safety and efficacy of new drugs and biologics in the pediatric population. The studies are to be performed on the same indication sought or approved for adult studies. Orphan drug indications are exempt from PREA. If the sought indication does not exist in a pediatric population, a waiver is able to be requested. Companies can postpone when studies are done after providing the FDA with distinct grounds for deferral along with a Pediatric Study Plan and timeline for proposed studies. While ideally pediatric studies should be initiated while adult development is ongoing, oftentimes studies may be delayed until adult studies are completed and sponsors feel that there are sufficient safety and efficacy data for them to start pediatric studies [9]. The Best Pharmaceuticals for Children Act (BPCA), from 2002 and updated in 2007, is a different aspect of expanding therapeutics for pediatrics with financial incentives for companies that voluntarily perform pediatric studies. These studies can be done to expand indications for drugs or on a moiety that may not have an indication. Orphan indications can be requested for study under BPCA [10, 11].

EXPANDED ACCESS

Unapproved products can also be used under Expanded Access or "compassionate use." It allows patients to have access to investigational products outside of clinical trials or if there is no safe or effective alternative for their medical condition or disease. Providers must consider that despite potential promising preclinical studies these drugs are ones that have not been approved or cleared as safe or effective by the FDA. There are 3 types of expanded access. There is emergency use access for a single patient, expanded access for intermediate-sized groups with a specific condition, and expanded access for widespread or treatment use for serious or life-threatening illnesses in the community. For any of these categories, depending on the product, 1 of the 2 types of regulatory submissions can be sought—an IND for a new drug/biologic or a protocol amendment to an existing IND. An emergency IND (eIND) and emergency protocol are meant for a single patient product use request for a non-approved product. The provider first requests use from the sponsor, and then the request is sent to the FDA and authorized by telephone or email to allow initiation of the drug as soon as given approval through this communication. However, an official written submission eIND/protocol must be submitted within 15 business days from the verbal authorization. Product use will also need IRB approval; however, in cases where there is not sufficient time for proper IRB review prior to starting treatment, the use of the investigation product must be reported to IRB within 5 working days. Intermediate-sized patient access is less common, and meant for populations

Table 1. Pathway of Development and Approval [4, 6]

Stage	Target	Intention	Average Years in Stage
Research and Development	Laboratory studies and computer modeling	Identify a potential drug compound	4
Preclinical	Animal studies and computer modeling	Verify drug activity and baseline safety	2
Phase 1	20-80 healthy volunteers	Establish drug dose and overall safety, understand kinetics	2
Phase 2	Ideally 100-300 patient volunteers	Confirm safety and establish efficacy benchmarks	2
Phase 3	Ideally 500-3000 patient volunteers	Gathering extensive therapy-related adverse events and comparing efficacy vs comparator	2
FDA Review (NDA/BLA)	Review of prior studies, computer modeling	Impartial review of data independent of sponsor for drug approval	1
Phase 4	Post-market product users	Longitudinal safety and efficacy surveillance	15

Abbreviations: BLA, Biological License Application; FDA, Food and Drug Administration; NDA, New Drug Application.

greater than 1 patient, but fewer than those met in a standard IND/protocol amendment. Unlike an eIND/protocol, the product may or may not be under development for marketing. For an intermediate-sized population IND, there is a 30-day waiting period to use the product unless the FDA clears the sponsor to provide product for use sooner. An intermediate-sized population protocol being added to an existing IND does not require a 30-day waiting period, but the protocol must be received and approved by both FDA and IRB prior to product use. An intermediate-sized IND tends to be for rare diseases or populations which will be difficult to recruit sufficient number of patients for a substantial trial. Expanded Access for Widespread use or a treatment IND is meant for a product

that is under active development for marketing and requires a 30-day waiting period before treatment is initiated unless FDA clears the sponsor for earlier use of treatment. The convalescent plasma and remdesavir for SARS-CoV-2 are 2 products which have been used in intermediate and treatment IND use before given Emergency Use Authorization (EUA) and afterward in populations that excluded in the criteria set for the EUA [12].

EMERGENCY USE AUTHORIZATION

An EUA is an allowance by the FDA Commissioner for public access to unapproved medical products or new indications of approved medical products to be used in an emergency

Table 2. Glossary of Terms

Term	Definition
Investigational New Drug	Sponsor provided compilation of drug data and analysis for the FDA to review and verify before beginning clinical research, including animal study data, toxicity data, manufacturing information, proposed clinical protocols, investigator information, and data from any prior human research
New Drug Application	Sponsor provided compilation of drug data and analysis for the FDA to review and verify for an indication, including preclinical studies, pharmacokinetics, clinical trials, proposed, labeling, safety updates, patient information, IRB compliance data, directions for use, and any international data on the product
Biologics License Application	Sponsor provided compilation of biologic or vaccine data and analysis for the FDA to review and verify for an indication, including preclinical studies, pharmacokinetics, clinical trials, proposed, labeling, safety updates, patient information, IRB compliance data, directions for use, and any international data on the product
FDA Review	A process in which a multi-specialty FDA team analyzes data of drug structure, safety, efficacy, benefit, and risk of a product for a given indication once a NDA is submitted
Standard Review	Review with a 10-mo goal for products not meeting criteria for shorter review time
Priority Review	6-mo goal and applies to products that fill a void or be a significant advancement from existing marketed products
FDA Approval	Data in NDA are reviewed and the product is determined to be effective for indication with benefit outweighing risk
Sponsor	A sponsor is an individual, company, or organization that initiates clinical study, ensures safe distribution of product, and is primary correspondence to both IRB and FDA.
Marketed product	An approved product that is manufactured and able to be distributed for consumer use. Companies may choose not to market a product after approval
Product Label	An accurate and objective compendium from the sponsor and refined by the FDA summarizing review data on the basis for approval, information on the best use of product, and safety precautions
Off-label	Use of a marketed or available product for an indication not specified in an approved label
Expanded Access	Expanded Access—known as “compassionate use”; allows patients to have access to investigational products outside of clinical trials, or if there is no safe or effective alternative for their medical condition or disease
Emergency IND (eIND)	A request made from a clinical provider to a product sponsor and authorized by the FDA for nonclinical trial use of a product still under investigation or not approved for a particular indication
Emergency Use Authorization (EUA)	Allowance by the FDA Commissioner for public access to unapproved medical products or new indications of approved medical products to be used in an emergency declaration as medical countermeasures in diagnosis, treatment, or prevention of serious/life-threatening diseases or conditions

Abbreviations: FDA, Food and Drug Administration; IRB, Institutional Review Board; NDA, New Drug Application.

declaration as medical countermeasures in diagnosis, treatment, or prevention of serious/life-threatening diseases or conditions. There are 4 statutory criteria for an EUA to be enacted (1) The chemical, biological, radiological, and nuclear (CBRN) agent must be serious or life threatening; (2) with data at hand there is some evidence of effectiveness; (3) there should be a positive benefit-risk analysis; and (4) there is no adequate, approved, or available alternative for the indication related to the CBRN agent. An EUA will still be set for specific age, weights, and indications as with drugs seeking approval. An EUA does not require specific training for investigators nor does it need IRB review or approval; however, it does require adverse event monitoring and record keeping of use. An EUA will typically stay in place for 1 year from the day it was enacted, though it can end, be revoked, or be revised based on the most up-to-date status of emergency and treatment. For example, hydroxychloroquine and chloroquine were granted an EUA on March 28, 2020, and once evidence indicated lack of benefit, the EUA was revoked on June 15, 2020. Also, an EUA does not grant automatic approval once the EUA ends, though the use of a drug through EUA will likely result in accelerated approval. Most of the products such as bamlanivimab, remdesivir, and convalescent plasma given EUAs for Covid-19 are simultaneously in the investigational process, with goals to have a marketable product even once the EUA ends [13, 14].

As noted, the parts played by the FDA and industry are well defined. A question to be asked is, what role can pediatric infectious diseases providers and researchers play? A big step is to be an advocate for drug development and stewardship. Providers should ask if the current drug armamentarium for a condition or disease is ideal. Knowing treatment limitations and understanding how care could be optimized with newer drugs, dosages, and delivery routes, while limiting adverse events, are important in advocacy. Product development is supported by having new clinical sites and working to have diverse study populations. Pediatric infectious diseases providers or institutions that use a product multiple times via eIND or for off-label use should push for the product to go for drug review and NDA for the indication. Providers should be open for partaking in studies and could potentially have trainees learn about the process as well. Institutions should also consider establishing provider time support and clinical space for studies. Providers can work with sponsors to understand gaps or limitations that are causing delays in the progression to NDAs; the FDA may be able to advise on combining efforts among institutions or modeling data to help hasten perceived roadblocks. As funding for clinical trials is often

lacking, it is important for physicians to work with sponsors to approach the FDA for accelerated approval or orphan drug status for qualifying products, as well as lobbying for legislature, which promotes funding constructs for products. The process of drug development is complex interwoven effort among scientists, patients, industry sponsors, FDA, and prescribing providers, with each group having a critical role to play (Table 2).

Notes

Potential conflicts of interest. The author certifies no potential conflicts of interest. All authors have submitted the ICMJE Form for Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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