The FDA Regulatory Process for Drug and Genetic Diagnostic Test Approvals

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In the United States as well as in other industrialized countries, prescription drugs must first be approved by the relevant regulatory agency. In the United States, the Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) is responsible for the review and approval of drugs. The core mission of CDER is to “assure that safe and effective drugs are available to the American people.”¹ In order to accomplish this mission, the FDA/CDER must work closely with the sponsors of drug products to assist them in performing appropriate studies and submitting the necessary evidence on which the approval is based. This regulatory process also draws on scientific advisors largely from the academic community, with congressional oversight mechanisms and a variety of advocacy groups with a vested interest in the approval process. The result of these complex and demanding interactions is that drug approvals are a public-private collaborative process. The purpose of this brief article is to familiarize academic investigators with the steps required to access the FDA drug product approval process, and, as a special case, to describe the possible routes of pursuing drug approval for pharmacogenetically targeted therapies.

It is in the interest of all medical researchers to be familiar with the FDA approval process for drugs and diagnostics so that they can either assist in the process when asked to do so or be prepared to access the approval mechanism on the discovery of potentially valuable treatments or diagnostics. It is critically important that in order to benefit society, biologic discoveries need to move beyond the pure scientific confines of experimentation and publication into a pathway that can culminate in commercial availability. For academic investigators, the drug approval process usually begins with identification and patent protection of intellectual property around a novel target or an actual new molecular entity (NME) capable of favorably interacting with a target. Another possible route to developing new therapies is via novel uses of already established drug classes or drug combinations. Intellectual property protection is mandated by federal law, through the Dole-Bayh Act passed in 1980.² The spirit of this law is that federally funded investigators need to repay society by translating their discoveries into something useful. The next step is to secure support for the early phases of development (e.g., for further target validation work) for preclinical or clinical early proof-of-concept studies or other testing that will establish the promise of the new therapy. Once that is done, the new NME or approach enters formal drug development in humans, typically subdivided into 3 phases.

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Before an unapproved drug can be tested in Phase 1 (first in humans), it must have an Investigational New Drug Application (IND) submitted to the FDA. An individual investigator (Investigator Initiated IND) or a corporate entity can apply for and receive an IND. To be granted an IND, preclinical safety data and information on drug product manufacturing are required, along with a rationale and protocol for the new therapy's use. Once dose-related safety and activity data are obtained in Phase 1 (typically in healthy volunteers, but Phase 1 can also be conducted in the potential disease indication), an end of Phase 1 meeting with the FDA is typically held to discuss the plans for Phase 2 based on the Phase 1 findings. At all stages of drug development, the FDA offers and encourages pre-Phase communication, including face-to-face meetings.

The purpose of Phase 2 drug testing is to define a potentially effective dose range that is not associated with limiting safety issues and to obtain efficacy information relevant to a Phase 3 study design. This is a critical stage of drug development, and in our experience it is often not given enough emphasis. The basis for the importance of Phase 2 is that the information obtained will be used to determine the critical components of Phase 3 study design, such as the dose(s) used, the clinical end points selected, and the initiation of a safety database. When the data are available from Phase 2, the important end-of-Phase 2 meeting is typically held with the FDA, at which several critical regulatory milestones are discussed and ideally agreed upon. These include whether the Phase 2 program is adequate for defining the dose(s) to be used in Phase 3, whether the Phase 2 data efficacy signals justify Phase 3, and the general design of a Phase 3 program. The Phase 3 development program must definitively defend the primary clinical benefit(s) of the NME. This usually requires 2 positive Phase 3 studies or 1 positive trial with a highly significant *P* value for a major clinical end point. In addition, the Phase 2 and 3 programs must provide an adequate safety database. Therapies designed to reduce morbid/mortal events usually include large, event-driven trials that acquire enough events to satisfy both safety and efficacy. However, development programs for symptomatic therapies may be relatively small and therefore require additional safety studies to rule out untoward safety concerns.

Following completion of Phase 3, a pre-New Drug Application (NDA) meeting is held, where the important aspects of the Phase 3 program are presented and discussed, and agreement is reached on whether (or not) the data could form the basis for drug approval.

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In the affirmative, an NDA is then prepared and submitted, and if it meets all the technical requirements,³ it is “filed” (accepted for review) 45–60 days later. According to the Prescription Drug User Fee Act, the FDA then has 10 months to render a decision on approvability.⁴ If an NDA has limitations for definition of clinical benefit, the safety concerns of the new therapy are not well understood, or a clear unmet need is not defined, then an advisory committee composed of academic experts, statisticians, and representatives from appropriate patient advocacy and industry groups is asked to review the NDA and recommend a course of action to the FDA.⁵ Another reason to convene an advisory committee meeting would be when the NME represents a new therapeutic direction, where scientific interpretation or even ethical issues require expert, interactive opinion.^{6–7}

For devices, which include diagnostic tests, review and approval are handled by another branch of the FDA, the Center for Devices and Radiological Health (CDRH). At the CDRH, there are 2 routes of possible FDA approval for a diagnostic test that is linked by an algorithm to prognosis or selection of candidates for therapy: a 510(k) or a Premarket Approval (PMA). A PMA differs from a 510(k) in that clinical efficacy data are required. The discussion here will be confined to a genetic diagnostic test that is coupled to use of a drug (pharmacogenetic targeting), something that has generated a great deal of recent interest from investigators, pharmaceutical and biotechnology companies, and the FDA. As clinical data are required to demonstrate the utility of such a test, the regulatory submission would likely be a PMA.

Although different divisions of CDER may have different approaches, currently within the Division of Cardiovascular and Renal Products (DCRP) of CDER, a drug approval with labeling linked to a genetic biomarker to identify responsive versus unresponsive subpopulations is handled by CDER/DCRP performing the NDA evaluation, CDRH the PMA (with the clinical data in the NDA serving as the clinical component of the PMA) review, and the Office of Combination Products serving to organize and expedite the process. To facilitate communication, all initial submissions for the combined product approval are submitted through DCRP. An advantage to this construct is that each review group performs the function with which it is accustomed, using principles and precedents that are well established. The only novel aspects of the review are the interpretation of the pharmacogenetic data, for which the FDA has a recently established a specialty group that can provide assistance.⁸

It is fashionable to criticize the FDA for the decline that has recently occurred in NME approvals.^{9–11} However, it is our position that this decline has everything to do with deficiencies in drug development and little to do with the regulatory process. Academic investigators interested in developing and commercializing their discoveries should be encouraged to access the FDA for assistance, where they will likely be pleased by the experience. **CTS**

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appropriately collect, analyze, and store genetic information to explain the variable responses that occur in clinical trials. A priority for the next several years is pediatric care. To begin, the FDA has invited a number of experts on sabbatical at the FDA to research the relationship between human ontogeny and drug metabolism. Other projects include outreach efforts towards healthcare providers and device companies and the exploration of bioinformatics. Dr. Huang believes more needs to be done with “gene expression, either to select patients or to see . . . how patients are responding to drugs.”

The FDA is constantly identifying needs and opportunities in the area of medical product development; fortunately, its collaborators have proved quick to respond to the call. As an associate editor for *Clinical Pharmacology and Therapeutics* until April 2008, Dr. Huang saw many warfarin manuscripts that addressed the questions the FDA and the summit had posed. Other FDA appeals for warfarin research involving race or pediatrics have also been answered by multiple organizations.

Dr. Huang sees the research focus shifting from determining genetic importance to discussions of implementation. She predicts the next step is a conversation not just among researchers but also within a larger community to address questions of reimbursement for medical products. In this way, the FDA hopes to lead U.S. healthcare down the critical path from initial investigation of these products to safe, effective medical treatment. **CTS**