The FDA drug approval process is onerous, requiring an extensive amount of time, funding, and testing. Drug manufacturers, driven by profit, attempt to receive special designations from the FDA to speed up the approval process and get their new drug on the market sooner. Four different faster options are currently available, affecting both the clinical trials and agency approval timeframes, with another option included in new legislation awaiting approval. According to Dan Kracov, a partner at Arnold & Porter LLP, critics of the faster pathways are concerned that patient safety may be compromised because drugs may be approved with less evidence regarding safety and effectiveness, but he believes that the benefits outweigh those risks. Expedited drug approval benefits patients who gain access to additional therapies but also offers broader benefits, Kracov said, as “many of the newer therapies are very targeted and produce outcomes that can potentially prevent years of costs due to chronic illness.” This Strategic Perspective examines the FDA’s approach to drug approval and considers what type of reform may come in the future.

The Current Process: Miles to Go

The current process contains three phases and 12 steps that must be completed to obtain approval for drugs for human use. According to the FDA, a drug is “any product that is intended for use in the diagnosis, cure mitigation, treatment, or prevention of disease; and that is intended to affect the structure or any function of the body.” Drugs differ from biological products, known as biologics, which replicate natural substances made from natural resources, such as enzymes, antibodies, or hormones. The regulation of biologics is handled by the FDA’s Center for Biologics Evaluation and Research (CBER) while drugs are evaluated by the FDA’s Center for Drug Evaluation and Research (CDER). The FDA does not test drugs and biologics—sponsors are responsible for conducting laboratory and animal testing.

Types of applications. There are three different types of new drug applications, and one for biologics. An investigational new drug (IND) application allows a sponsor to seek exemption from the requirement that the drug have an approved marketing application before it is moved across state lines. This exemption is necessary for an investigational drug to be sent to different clinical investigators.

A new drug application (NDA) is submitted only after a sponsor has collected sufficient evidence of a drug’s safety and effectiveness. This evidence is obtained through animal studies and human clinical trials of an IND. The NDA should contain enough information to allow the FDA reviewer to determine that a drug is or is not safe and effective, whether the benefits outweigh the risks, if the labeling is appropriate and complete, and if manufacturing methods and controls are adequate. The NDA must be accompanied by documentation about testing, ingredients, how the drug behaves, and how it is manufactured and packaged.

Generic drugs are approved through an abbreviated new drug application (ANDA), which does not require the same safety and effectiveness data that accompanies an NDA. Generic drug applications must demonstrate bioequivalence with the brand name drug, meaning that it performs in the same manner. This manner of approval was established through the Drug Price Competition and Patent Term Restoration Act of 1984 (P.L. 98-417), also known as the Hatch-Waxman Act.

Over-the-counter (OTC) medications are handled differently because of the massive amount of marketed OTC drug products (over 300,000, according to the FDA). These drugs are broken down into 80 therapeutic classes, and each class has a drug monograph published in the Federal Register. Monographs contain information about what is acceptable for a particular class, including ingredients, doses, labeling, and formulas. If a new product conforms to a monograph, it does not need to receive further review prior to marketing; however, those that do not conform must be reviewed as an NDA.
Biologics are approved through a therapeutic biologic application (BLA). Biologics are licensed through section 351 of the Public Health Service Act (PHS Act). Like other applications, BLAs require a showing that the product, manufacturing process, and manufacturing facilities protect the safety and efficacy of the biologic. The BLA also must contain information about the purity and potency of the biologic.

**Preclinical and clinical testing.** Drug sponsors must first conduct preclinical testing in animals, which can take three to four years, to obtain the necessary data to include in an IND for the FDA to grant approval to move forward on human testing, or clinical studies. A local institutional review board (IRB) can approve, order modifications to, or disapprove research. This board, made up of both scientists and nonscientists in research institutions (or hospitals), ensures that those participating as research subjects are protected. IRBs approve protocols, such as the type of people who may serve as research subjects, the length of the study, the medications and dosages involved, and objectives.

Phase One testing, as described in 21 C.F.R. section 312.21, includes somewhere between 20 to 80 volunteers. According to Pfizer, Phase One subjects are typically healthy volunteers, although for some medication this phase is made up of subjects who have the disease the medication is designed to treat. This phase is typically short, as the purpose is to determine what the potential side effects, toxicity, and dosage ranges should be. This phase allows researchers to analyze some of the potential risks of the drug and determine if development should continue. This phase emphasizes safety, and if the toxicity levels are found to be acceptable, Phase Two begins.

Phase Two focuses on effectiveness in people who have the disease or condition the medication is designed to treat. In most studies, patients either receive a placebo or the actual drug studied, and the results are compared. According to CenterWatch, a company that provides extensive clinical trials information to both professionals and patients, this phase involves hundreds of subjects and can last up to two years. Of all drugs that enter Phase One and Phase Two testing, only about a third of them successfully complete both phases.

Those drugs that move on to Phase Three studies are studied in as many as thousands of patients. According to Medscape, Phase Three trials can last up to a decade. Once sufficient data is obtained, the sponsor can submit the NDA. The FDA then completes an independent review and makes recommendations. The review time was shortened by the Prescription Drug User Fee Act (PDUFA), which allows the FDA to collect fees from pharmaceutical manufacturers to enhance the review process. A standard application is reviewed within 12 months, while a priority application is reviewed in half that time. If a drug is approved, sometimes the FDA requires Phase Four testing even after the drug is put on the market. According to a Perspectives in Clinical Research journal article, Phase Four testing is an important phase of development, as it is the first chance to observe effectiveness in a real-world setting.

**Speeding Up the Process**

According to the Tufts Center for the Study of Drug Development (CSDD), the cost of developing an approved prescription drug has increased 145 percent, adjusted for inflation, since 2003. Scientific American reported in November 2014 that pharmaceutical companies spend about $1.4 billion out of pocket to develop and test drugs and forego about $1.2 billion in returns during the decade a drug spends in development, while Phase Four developments can cost another $312 million. Unsurprisingly, pharmaceutical companies are very interested in pursuing options that allow them to seek approval faster, with lower up-front costs. In an interview with Wolters Kluwer, Alexander J. Varond, an associate at Hyman, Phelps, & McNamara PC, pointed out that the type of designation received is typically determined by the stage of drug development or review, such as preclinical data or a clinical demonstration that a therapy shows a great deal of improvement over therapies that are currently available.

**On the Fast Track.** One option for faster review is known as Fast Track designation, made available by section 506(a) of the Food, Drug, and Cosmetics Act (FDC Act). A sponsor can request this designation at any point during development. This option is limited by the FDA to drugs that fill an unmet medical need and treat serious conditions. The FDA considers many diseases to be serious conditions, including AIDS, cancer, depression, and epilepsy. The FDA admits that the decision is a “matter of judgment,” but considers whether a drug will have an impact on day-to-day functioning, survival, or preventing the condition from becoming more severe. Additionally,
a drug deserving of Fast Track designation must be able to fill an unmet need when no therapy currently exists, or potentially offer a better option than available therapies. Certain indications of possible advantages over existing therapies include superior effectiveness, less serious side effects, improving the diagnosis in conditions where early diagnosis improves outcomes, or decreasing toxicity compared to available therapies.

When a drug receives a Fast Track designation, the following benefits may be available during the development and approval process:

1. more frequent meetings with the FDA regarding the development plan;
2. more frequent written communication regarding the design of trials;
3. eligibility for the Accelerated Approval and Priority Review tracks;
4. rolling review, allowing a sponsor to submit sections of the NDA or BLA instead of waiting until the entire application is complete.

A Rho® white paper suggests, however, that the Fast Track might not be very beneficial. David Shoemaker, Rho’s senior vice president of research and development, points out that the FDA already provides many opportunities for meetings during the development process, as well as follow-up and technical meetings, plus adequate correspondence. Additionally, NDAs always have been allowed rolling review, and drugs and biologics that meet certain standards are eligible for Accelerated Approval even without Fast Track designation. Ultimately, Shoemaker believes that a Fast Track designation does little to speed up the development process.

We’ve had a Breakthrough (Therapy). Another speedier pathway through the approval process is Breakthrough Therapy. This method is reserved for drugs that treat a serious condition, with clinical evidence showing that the drug may have a marked improvement on significant endpoints over therapies that are currently available. Determining substantial improvement depends on the magnitude of the treatment’s effect, and how important the observed clinical outcome truly is. When determining whether a drug should receive a Breakthrough Therapy designation, a clinically significant endpoint will relate to irreversible morbidity or mortality (IMM), or symptoms representing serious consequences. The FDA will look for findings such as an effect on a surrogate endpoint or intermediate endpoint reasonably likely to predict a benefit, an effect on biomarkers that suggests the potential for meaningful effect, or an improved safety profile over an available therapy that has similar efficacy. According to the National Cancer Institute at the National Institutes of Health, a surrogate endpoint allows the efficacy of a therapy to be measured sooner than a true clinical endpoint, which may take a much longer time to measure. For example, in a cancer drug trial, a surrogate endpoint might be a shrinking tumor whereas the stronger indicator is improved quality of life, or longer survival. Surrogate endpoints, however, are not always completely reliable. The FDA describes a surrogate endpoint on its Accelerated Approval pathway page as a measure that is thought to predict a benefit. The difference between the FDA’s description of a surrogate endpoint and an intermediate clinical endpoint is subtle, with an intermediate endpoint defined as a “measure of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug.” An example of an intermediate endpoint is an effect on IMM, or, according to Varond, an improvement in muscle strength.

A Breakthrough Therapy designation allows a drug to receive the features of a Fast Track designation as well as additional FDA input on designing an efficient development program and organizational commitment. Although a drug company must request the designation, the FDA may suggest that the request be submitted. For the greatest effect, a designation request should be received by the FDA by the end of phase 2 meetings. Varond notes that “breakthrough therapy designation is available to sponsors later in the drug development process than fast track designation because, unlike with fast track designation, at least some clinical evidence is required.”

Step on the gas: Accelerated Approval. The Accelerated Approval pathway is wholly based on surrogate endpoints and intermediate clinical endpoints. This pathway was created in 1992 as a response to the extended period of time required to observe a drug’s clinical benefit and is limited to drugs for serious conditions that fill an unmet medical need. In 2012, the Food and Drug Administration Safety Innovations Act (FDASIA) amended the FDC Act to include an effect on intermediate clinical endpoints as a basis for accelerated approval. The acceptance of a proposed surrogate or intermediate clinical endpoint is based on scientific support. The FDC
Act requires effects to be “adequate and well controlled.” If the FDA approves a drug based on evidence of tumor shrinkage, a drug company must continue “phase 4 confirmatory trials” to confirm that the tumor shrinkage predicts a longer life.

In his paper, Shoemaker noted that the Accelerated Approval designation focuses on shortening the research time prior to approval, not on the actual approval timeframe. Additionally, if phase 4 testing shows issues with efficacy or safety, marketing approval may be revoked or the FDA may grant the designation with restrictions, such as determining that specially trained physicians are the only ones who can prescribe the treatment.

Make it a Priority (Review). The Priority Review designation sets a six month FDA goal for action on an application as opposed to the 10 month Standard Review goal. This designation is reserved for drugs that would significantly improve the safety or effectiveness of treating, diagnosing, or preventing serious conditions over the current approaches. To demonstrate significant improvement, a sponsor must show evidence of increased effectiveness, elimination or substantial reduction of a drug reaction, documented enhancement of patient compliance, or evidence regarding a new subpopulation. A Priority Review designation has no effect on the clinical trial period, scientific/medical standard for approval, or the quality of evidence required. According to Shoemaker, a sponsor should discuss this possibility at the pre-NDA/BLA meeting.

What does the industry think?

Data released by the FDA and compiled by the New England Journal of Medicine (NEJM) indicated that 55.6 percent of drugs in development in 2013 qualified for at least one designation. As a result, Dr. Kesselheim of Harvard Medical School believes that the “exceptions are beginning to swallow the rule.” In a May 1, 2015, New York Times article, he said that the pathways were intended to be reserved for urgent circumstances and expressed worry that the pathways are now too popular. This means that more drugs stand to be approved based on less evidence of efficacy and safety. However, some experts think that the faster pathways can be utilized without compromising safety. Varond pointed out that while drug approval based on less data is true in some cases, “it is not true when faster approval is the result of greater efficiencies, better planning, and increased investment of capital and personnel.”

21st Century Cures. Legislation introduced in late April 2015 by Congressman Fred Upton (R-Mich), known as the 21st Century Cures Act, would provide more options to speed up the approval process. According to an April 30, 2015, New York Times article, an earlier draft of the legislation involved a more aggressive approach to streamlining drug approval and gave drug companies more power to market drugs for off-label uses and extended the period of exclusivity for brand name drugs. These provisions as well as “considerable micromanaging” of the FDA were removed. This is an important change, as according to Kracov, the “FDA’s current approach to the dissemination of off-label information is becoming increasingly untenable” in light of First Amendment case law, but has not been changed due to fear that the approval process would be affected (see Off-label drug use marketing—is more information a bad thing?June 23, 2015). He suggested that the FDA and potentially Congress develop a more usable approach to speech about off-label uses and explore alternatives that would allow more transparency for physicians and patients.

The pared-down bill was offered following hearings and table meetings at which comments were solicited. Although critics of the bill expressed safety concerns, supporters lauded the collaborative efforts that resulted in the presented draft. The current legislation contains room for an approval path for “dormant therapies” that is not yet described. A program for antibiotics limited to specific populations would allow for faster review. According to the Committee on Energy and Commerce, health data obtained through research and trials would be more easily shared, and patient generated registries would allow for easier recruitment for participation in trials. An FDA official, Dr. Janet Woodcock, testified about the bill before the House of Representatives, but expressed concerns about the additional work that would be required of the agency on the existing budget to the New York Times as reported in the April 30 article.

Future developments. Like Woodcock, Kracov also brought up the issue of resources, mentioning that the agency must spend resources to ensure that the expedited review processes work properly; yet, he believed that the agency has been successful in adapting to the use of these pathways. Kracov viewed the goals of
21st Century Cures as a reflection of the industry’s current debate on approval system reform, which “focus[es] on using all available data and scientific tools to support review and approval processes.” This includes faster validation of biomarkers and clinical endpoints as well as the use of more real world data. He stressed that certain provisions in the Act could be stronger, noting that the legislation simply urges the FDA to provide additional guidance on biomarkers and endpoints without establishing particular requirements. Nevertheless, Kracov finds these provisions to be “an important step” in the process. When asked what reform of the approval system would look like, he stated that he does not foresee a large change to the current standard, but “targeted steps to make the current standard more achievable,” pointing out that the approval process is under constant, but incremental reform. Areas of concern involve developing a more patient-focused approach to development and approval, as well as ensuring that the agency embraces technological developments and their opportunities. Varond echoed some of these opinions, noting that the FDA should better integrate patient feedback about risks and uncertainty, and the agency could take more steps to improve translational sciences and use more regulatory tools, such as identifying more unvalidated surrogate endpoints for sponsors to use.

Varond believes that the FDA could make more use of Accelerated Approval pathway, stating that it “represents one of the single biggest opportunities for reform in the drug approval process.” He pointed out that the FDA has approved fewer than 20 therapies for noncancer and non-HIV/AIDS indications since 1993. Using Accelerated Approval for more of these drugs would allow for the development of cures for diseases with late clinical endpoints, such as Alzheimer’s disease, Varond said. In his view, this pathway is vital to producing therapies for certain diseases as sponsors are not economically inclined to invest in therapies for diseases that take years to show clinical benefit. He added that “researchers should continue their efforts to gather evidence on unvalidated surrogate endpoints for diseases, and the FDA should exercise the flexibility needed to approve...therapies that take years to reach clinical endpoints.” He also cautioned that for this to happen, the agency must focus on clarifying the differences between unvalidated and validated surrogate endpoints. Drugs approved based on unvalidated endpoints are provided conditional approval, while those based on validated endpoints, such as levels of cholesterol and blood pressure, are given full approval. Because the terms are frequently confused, Varond thinks that regulators “impose barriers on Accelerated Approval that are too high.” According to Varond, the 21st Century Cures Act has brought attention to the need to expand the use of Accelerated Approval and focus resources on looming public health crises related to Alzheimer’s disease and treatment-resistant antibiotic strains.

Conclusion
As more and more drugs move through these faster pathways, it is increasingly important to safeguard the delicate balance of protecting patient safety and facilitating the faster availability of potentially life-saving therapies. The FDA and the legislature have the difficult task of balancing input from patient advocates seeking alternative therapies, physicians concerned about the possibility of unknown risks, and pharmaceutical companies seeking speedy approval to ensure profitability. The agency must continually adapt and improve its processes, spend resources appropriately, and promote patient involvement.

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