FDA and Accelerating the Development of New Pharmaceutical Therapies

Introduction

In 1962, the United States was shocked by the news that thousands of babies were being born in Europe with terrible birth deformities, caused by a drug known as thalidomide, that was prescribed to European women during pregnancy. While the U.S. was spared this calamity by the refusal of the Food and Drug Administration to allow thalidomide's sale in this country, Congress saw the horrifying effects of inadequately reviewed drugs and unanimously enacted legislation directing the FDA to tighten the standard by which new drugs were approved for marketing – with a requirement for drug companies to submit solid and rigorous science-based evidence that new drugs were both safe and effective.

More recently, Congress has passed laws, including the 1992 Prescription Drug User Fee Act, designed to add a new focus - bringing important drugs to market more quickly and predictably, while still protecting Americans from unsafe and ineffective medicines. Congress' focus on optimizing speed of access as well as safety and effectiveness is challenging but necessary – both are critical to the health of American patients. And the success of the biopharmaceutical industry depends on both as well. Market strength depends on American and worldwide confidence in the quality and rigor of FDA's oversight of drug safety and effectiveness, while continued development of innovative new drugs is aided by a swift, predictable approval process.

This white paper provides up-to-date information on FDA's drug approval process, demonstrating that FDA continues to review and provide Americans with access to innovative drugs more quickly than the EU and other developed countries. The paper also describes how FDA is using available tools to expedite drug development, including Accelerated Approval, flexible clinical trial designs, surrogate endpoints, Priority Review, Fast Track Designation, and Breakthrough Therapy Designation.

Drug Review Today

The results of the improvements in FDA's drug review process have been remarkable. Over the past two decades, the time required for FDA review has decreased from years to months – and the Agency has become the acknowledged leader among the world's regulatory agencies in both the number of new drugs approved each year and in the timeliness of review. Today it remains the world's leader. More specifically,

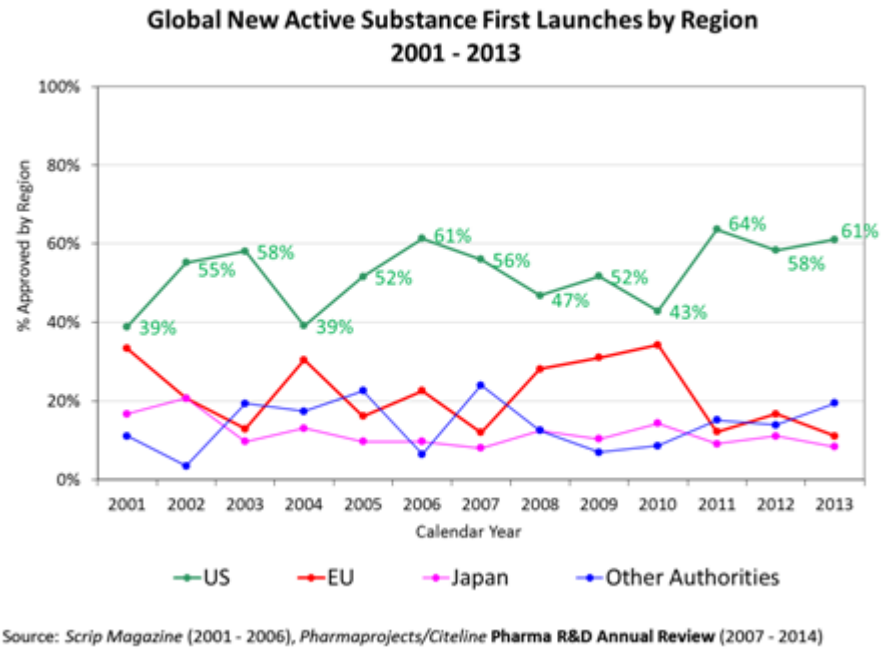
- In 2013, FDA approved 35 new molecular entity drugs or NMEs (drugs that contain an active ingredient that has never previously been approved by FDA) and original biological products (27 products were approved by FDA's Center for Drug Evaluation and Research or CDER and 8 by FDA's Center for Biologics Evaluation and Research or CBER). The drugs included advances in the treatment of rare forms of cancer and a "game-changing" cure for Hepatitis C. These approvals were on par with the average of 26 NME approvals a year seen in recent years.[1]
- In 2014, the pace of drug approval was even stronger: FDA approved 51 new molecular entities and new biological products (41 by CDER and 10 by CBER). Additionally, the number of orphan drugs approved (21) and novel therapeutic biologic products approved in 2014 (21) reached all-time highs.
- Average review times by FDA have been consistently faster than regulatory agencies in other countries.[2] Indeed, 76 percent of the new drugs approved by Japan, EU and FDA from 2009 to 2013 were approved first by FDA, according to a report released in May by the British-based Centre for Innovation in Regulatory Science.
- Yet another independent analysis concludes that FDA continues to lead the European Union and other advanced regulatory authorities in the introduction of novel new drugs,[3] as shown by the graph below. In the years 2011-2013, the number of novel

[1] "Novel New Drugs 2013 – Summary," U.S. Food and Drug Administration, January 2014[2] Downing NS et al. "Review of Novel Therapeutics by Three Regulatory Agencies," New England Journal of Medicine, September 20, 2012, pp. 1165-1167; *and* "New Drug Approvals in ICH Countries, 2004-2013," Centre for Innovation in Regulatory Science, R&D Briefing 54, 2014

[2] Downing NS et al. "Review of Novel Therapeutics by Three Regulatory Agencies," New England Journal of Medicine, September 20, 2012, pp. 1165-1167; *and* "New Drug Approvals in ICH Countries, 2004-2013," Centre for Innovation in Regulatory Science, R&D Briefing 54, 2014

[3] In addition to approval times, in Europe new drugs must go through a separate review process for making reimbursement decisions, which typically further delays patient access to new therapies.

drugs launched first in the U.S. approached an all-time high, with roughly 60% of novel drug introductions occurring in the U.S. first,[4] providing earlier access for U.S. patients:

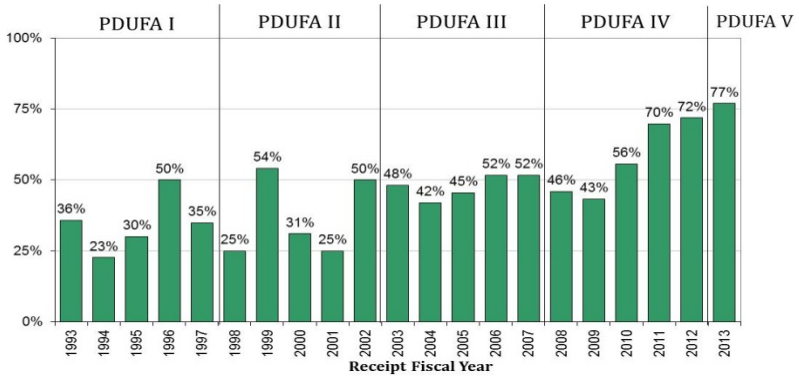


Source: *Scrip Magazine* (2001 - 2006), *Pharmaprojects/Citeline* **Pharma R&D Annual Review** (2007 - 2014)

FDA and industry have also made important progress in reducing the number of review cycles required for approval after initial submission – further reducing review timelines. A high failure rate for initial submission of new drug applications was a vexing problem plaguing both industry and the FDA for many years. Indeed, in the early years of the drug review user fee program that began in 1993, two-thirds of applications for new molecular entities were not approved by the agency after review of the initial submission. FDA took lessons from the high failure rates, and applied them to subsequent products. As a result of better collaboration between the industry and the agency, "first cycle" approvals are exceeding 70%, without any decrease in FDA's approval standards. These improvements in first cycle approval rates translate into patients gaining earlier access to important new drugs and lower costs for industry and the agency. The chart below illustrates this important trend over the life of the Prescription Drug User Fee (PDUFA) program.

[4] Scrip Magazine (2004 - 2006), Pharmaprojects/Citeline Pharma R&D Annual Review (2007 - 2014)

FDA First Cycle Approval Rates



Competitiveness of the U.S. Drug Industry

Streamlining the efficiency of the drug development process is in everyone's interest. American patients are realizing the benefits of FDA's success in drug reviews because, in most cases, they are the first in the world to receive life-saving treatments for cancer and other serious diseases. A responsive regulatory review program has allowed the pharmaceutical industry to continue to flourish, which in turn has benefitted the overall U.S. economy. For more than a decade, pharmaceutical company research and development has remained steady and strong, both as adjusted by inflation and as a percentage of sales, even during the economic downturn. While two million manufacturing jobs were lost during that time, less than 15,000[5] pharmaceutical jobs were lost, and pharmaceutical sales continued to keep pace with pre-recession levels.

Stock performance is another measure of the economic health of this industry. For many years, the stock performance of pharmaceuticals has outstripped other industry segments, indicating robust investor confidence in the industry's ability to remain competitive and profitable. For example, from May 2012 to May 2014, the Standard & Poor's 500 saw a remarkable 40% increase in value while pharmaceutical stocks performed at *double* that rate. FDA's reputation as the "gold standard" for drug reviews correlates with U.S. pharmaceutical manufacturers'

[5] Barker, Megan M., "Manufacturing Employment Hit Hard During the 2007-2009 Recession," Monthly Labor Review, Bureau of Labor Statistics, U.S. Department of Commerce, April, 2011

success. Countries with less rigorous standards generally do not have strong pharmaceutical industries, and physicians around the world write prescriptions for FDA-approved drugs with confidence in those drugs' safety and effectiveness.

FDA and Drug Development

Not only has the FDA drastically reduced its review time, it has also worked with industry to reduce overall drug development time by engaging earlier with the developer to discuss flexible approaches to developing data needed for approval. FDA's review time represents a small fraction of total drug development time; the process of discovery and testing takes far longer. In the 1970s and 1980s, when patients and industry were concerned about a drug "lag" with Europe, FDA's drug review program was so modestly funded that the agency could do little more than await a company's application for approval and place it into a queue for eventual review. Today, thanks to staffing increases supported by industry user fees and new regulatory authority, FDA is quicker and more nimble. Additional resources have enabled FDA to contribute insight and expertise to accelerate drug development and assist and encourage new drugs sponsors. New initiatives adopted concomitantly with the introduction of user fees are further reducing drug review times and substantially lowering drug development times:

Accelerated Approval – This program, begun in the early 1990s, enables FDA to speed new treatments for serious or life-threatening illnesses for which there are no adequate therapies. Accelerated Approval is usually based on a "surrogate endpoint" -- that is, a "biomarker" that is "reasonably likely… to predict clinical benefit." Clinical benefit will be verified through additional studies conducted after approval. More specifically, a surrogate endpoint is a marker of drug effect (e.g., an effect on blood pressure, a lab value, or tumor size) that does not directly represent an improvement in how a patient feels or functions, but is expected to predict such a benefit. The earliest surrogate endpoints included tumor shrinkage in cancer patients and an increase in certain white blood cells ("CD4" cells) in AIDS patients. Accelerated Approval was designed to speed the delivery of new drugs to patients with serious conditions -- and limited treatment options -- with verification of clinical benefit provided in "Phase 4" post-approval testing. Since its creation, the accelerated approval program has been used to approve over 90 new drugs and biologics, about a third for AIDS, a third for cancer, and a third for a variety of other serious conditions.

Use of Surrogate Endpoints in Traditional Approvals – Once it is known that a surrogate endpoint predicts clinical benefit, the surrogate endpoint can also be used to support traditional approvals. Indeed, of the 94 new drug applications approved by FDA in calendar years 2010 through 2012, 45% were approved on the basis of a surrogate endpoint known to predict clinical benefit and the majority of these were traditional approvals. For example, FDA regularly approves drugs for diabetes treatment based on a "biomarker" -- i.e., effects on a laboratory test (the HbA1C test, a measurement related to average levels of sugar in the blood); for control of hypertension based on effects on blood pressure; and for control of abnormal lipids based on blood measures of cholesterol.

Priority Review – Drugs that hold the promise of delivering a significant improvement over existing therapy for serious or life-threatening illnesses can be designated for "priority" review, and a shortened six-month FDA review goal. From January 2008 through December 2013, 86 new drugs and biologics approved by FDA received priority status.

Fast Track Designation – FDA can provide Fast Track Designation to drugs for serious or life-threatening illnesses for which there is an unmet need, including no approved treatments. Once designated, FDA works more closely with drug sponsors to facilitate submission of acceptable drug development plans, clinical trial designs, and data collection methods to support FDA review of the products' safety and effectiveness. Once the sponsor begins to develop its marketing application data, it can submit the data to FDA for "rolling review," rather than the usual process of submitting the entire marketing application at once. From January 2008 through December 2013, 66 new drugs and biologics approved by FDA received Fast Track Designation.

Breakthrough Therapy Designation – In 2012, Congress directed FDA to establish another program for expediting the development and review of new drugs for serious conditions, where there is preliminary clinical evidence that the drug may provide substantial improvement over existing therapy. Drugs that receive "Breakthrough" designation receive intensive guidance on an efficient drug development program, beginning as early as Phase 1. FDA makes an organizational commitment to involve senior managers and experienced review and regulatory health project management staff in a proactive, collaborative, cross-disciplinary review for such drugs. Although this program is new, 13 new drugs and biological products that received the

Breakthrough designation have already been approved by FDA. And as of December 31, 2014, 74 had been granted the designation across a range of needs – cancer, infectious diseases and orphan diseases. The concept is expected to be a significant additional tool for reducing development times for such high impact drugs.

Flexibility Regarding Evidence Required to Support Approval – The statutory requirement for approving a new drug is that it be shown to be safe and effective. Effectiveness must be based on substantial evidence from adequate and well-controlled clinical investigations. This requirement usually means evidence from at least two adequate and well-controlled studies, each convincing on its own, although a single study can be sufficient. The agency "exercise[s] the broadest flexibility in applying the statutory standard, while preserving appropriate guarantees for safety and effectiveness," as its regulations state.

In fact, more than one-third (69) of the new drug applications approved by CDER from 2008 through 2013 were approved on the basis of just one human study and supporting evidence. This included 167 novel drugs, some with multiple indications (for a total of 184 new indications). As a recent analysis by scientists from Yale University and the Mayo Clinic concluded:

> *"Such regulatory flexibility allows for a customized approach to approval, including the ability to rapidly approve potentially effective therapies for life-threatening diseases, such as certain cancers, or those diseases for which there is no existing effective treatment, such as orphan diseases."*[6]

These many innovative and flexible approaches underscore FDA's commitment to making drugs that are shown to be safe and effective available as rapidly as possible. Taken as a whole, of the 184 new drugs applications approved by FDA from 2008-2013, almost two-thirds (112) were found to either have characteristics of a flexible development program and/or engaged in one or more of FDA's expedited development programs (fast track, breakthrough, accelerated approval, priority review) – without undermining or diminishing FDA's commitment to a strong safety standard.

[6] Downing, NS et al, "Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005-2012," Journal of the American Medical Association, January 22, 2014, pp. 368-377.

Rare Diseases

Nowhere is the use of flexibility in drug development more evident – and impactful - than in the case of rare, or "orphan," diseases that afflict a small percentage of the population and are, therefore, not as commercially attractive for product developers. Yet finding effective treatments for rare diseases is a public health priority, and FDA has brought to bear all of its drug review and technical assistance tools to assist the development of new treatments for these conditions. The data on FDA's involvement with rare diseases largely speaks for itself:

- As noted previously, the number of orphan drugs approved (21) and novel therapeutic biologic products approved in 2014 (21) have reached all-time highs;
- 80% of drugs approved for orphan diseases from 2008 through 2013 utilized at least one of FDA's expedited review programs;
- 62% of the novel new drugs for orphan diseases were approved on the basis of just one clinical trial plus supporting evidence; and,
- 25% of the new drugs for orphan diseases were approved on the basis of a novel endpoint, endpoints for which there had been no prior precedence for the basis of approval in any disease.

The statistics illustrate FDA's commitment to utilize all available tools to assist drugs for rare disease in getting "over the finish line."[7]

"Targeted" Drug Development

Personalized medicine, which enables predictions of how individuals will best respond to specific drugs and customized treatments, offers one of the most promising areas for advances in drug development. FDA is working in collaboration with researchers, manufacturers of drugs and biologics, health care professionals and others to better understand and adapt to the promise of personalized medicine, and has many ongoing efforts to work toward this goal. However,

[7] The Orphan Drug Act also provides financial incentives, such as tax credits, to orphan drug sponsors which further assist in their development

considerable work still needs to be done to realize its promise and the President has proposed to further spur development through his Precision Medicine Initiative, unveiled on January 30.

"Targeted drug development" is a growing area of drug discovery. It is the identification of patients for inclusion/exclusion either in the pivotal studies supporting approval or for the drug's use in the labeled indication based on a genetic test, biomarker, or susceptibility test (e.g. bacterial resistance, tumor genetic mutation). These treatments are specifically "targeted" to treat patients that are most likely to respond, or more safely receive, the medication based on specific tests. In the early 1990s, only 5% of FDA's new drug approvals were for targeted therapies. Twenty years later that number had risen to a quarter of new approvals, and in 2013, approximately 45% of FDA's approvals were for targeted therapies. For example, several very important new targeted treatments for cancer – such as Mekinist and Tafinlar (for forms of melanoma), Imbruvica (for forms of lymphoma and leukemia), and Zykadia (for a form of lung cancer) – have been approved recently, and the use of targeted therapies is clearly expanding rapidly. Indeed, approximately 80% of new compounds designated by FDA as "Breakthrough" therapies are targeted.

FDA's Advisory Role in Drug Development

One of the most significant changes in FDA's drug review program – an important outcome of FDA and industry user fee negotiations – is the agency's growing ability to provide considerable expertise in clinical trial design to aid drug developers. Through meetings between the agency's and sponsor's medical and scientific experts, often early in the development of a drug ("pre-IND" and "end of Phase 1"), and at critical later times, the sponsor can gain valuable advice about planned clinical trials, development milestones, and data requirements. Such early and frequent communications were not possible before user fees were established, but additional resources have infused hiring, training, and energy.

Evidence suggests that early and frequent communication between sponsors and the FDA can significantly reduce overall drug development times. For instance, in an analysis of the 184 new drug applications approved from 2008-2013, for the 67 drugs that were the subject of a Pre-IND meeting, the median clinical development time was only 6.6 years as compared to 8.0 years for drugs that did not have such meetings. Similarly, drug development was slashed by more than a

year for companies that sought an End-of-Phase I meeting with FDA, compared to companies that did not request such meetings; and companies that had End-of-Phase II meetings with FDA had higher first cycle approval rates. This analysis includes drugs that were not part of an expedited development program.

Adaptive Trial Designs

FDA is also actively involved in working with sponsors to help develop adaptive trial designs, including designs with Bayesian methods[8] based on interim assessments of biomarkers planned and specified ahead of the initiation of the study. Using this approach, the agency is searching for ways to address the unique questions being asked in a way that is as efficient as possible but still gives FDA confidence in the results. The goal of these designs is to reduce the size and duration of the trial, demonstrate an effect if one exists or provide broader dose-response information. These adaptations are performed with close attention to statistical rigor.

The use of Master Protocols is another novel approach. The Lung Cancer Master Protocol, or Lung-MAP, is a multi-drug, multi-arm, biomarker-driven squamous cell lung cancer clinical trial that uses genomic profiling to match patients to investigational treatments that may target the genomic alterations, or mutations, found to be driving the growth of their cancer. Based on these results, patients are assigned to one of five different study arms – each testing a different drug from a different manufacturer.

Over time, treatments can be modified based on response and additional drugs can be added, while others can be dropped. Combining the resources of several drug companies to test several therapies both strengthens our knowledge base and improves the likelihood that a patient will receive a drug that will work for them. Lung-MAP is a public-private collaboration with FDA, NCI, patient advocacy groups, the drug industry, and academia.

FDA's Critical Path Initiative

In addition to the efforts previously discussed, FDA recognizes the vital importance of advancing the science of drug development generally. In 2004, FDA launched the "Critical Path Initiative,"

[8] "Bayesian" methods refer to a type of statistical probability that predicts the likelihood of a future event. In drug review, it can help drug reviewers to predict if interim evidence of a drug's safety and efficacy is likely to be borne out by further study.

to address the widening gap between scientific discoveries and their translation into innovative medical products. Critical Path challenges FDA, industry, and the greater scientific community to work more closely together to improve the drug development process. For example, Critical Path supported the founding of the Clinical Trials Transformation Initiative, a public-private partnership whose goal is to improve the quality and efficiency of clinical trials – thus speeding the development of new drugs at lower cost to industry. This initiative addresses the biggest cost driver in drug development – the planning and conduct of large clinical trials – including patient identification, screening, and enrollment.

Advancing Regulatory Science

Rapid developments in technology and scientific discovery are creating increasingly complex products. To keep pace with these developments, over the past several years the FDA has been striving to further develop regulatory science: the knowledge, methods, standards, and tools needed to increase the certainty and consistency of regulatory decisions and improve the translation of basic discoveries to viable medical products.

Accordingly, the agency has been investing in regulatory science in many ways, building on the achievements of existing agency programs, like the Critical Path Initiative. For example, FDA has been ensuring the agency's readiness to evaluate emerging technologies, modernizing its toxicology programs, stimulating innovation in personalized medicine, and harnessing diverse IT data to improve health outcomes. Those efforts are already bearing fruit – i.e., through new ways of analyzing data to predict patient treatment for Hepatitis C; new computational toxicology modeling for vaccine safety that will improve vaccine use worldwide; and a new database to assess potential drug interactions mediated by a specific class of proteins.

Conclusion

Advancing the health of Americans through the development of safe and effective new drugs is an imperative at the heart of FDA's mission. The infusion of resources provided through industry user fees has enabled FDA to adapt to rapid advances in science and to dramatically cut drug review times to speed promising therapies to patients. In the 21st century, FDA is the fastest drug review agency in the world.

FDA has worked effectively to implement flexible review practices without lowering the agency's standard for drug efficacy. This flexibility has translated into a historically high proportion of drug approvals on the first regulatory review cycle, increasing predictability for drug developers. These changes resulted in faster drug review times relative to other regulatory authorities and an increasing proportion of new medicines being introduced in the U.S. first, allowing for earlier access to innovative treatments.

Recently, rapid advances in our understanding of human biology and the underlying mechanisms of some diseases have offered many new potential targets for medical product development. But we still have a long way to go in understanding the full range of diseases that confront Americans and in developing the scientific tools necessary to translate scientific discoveries into treatments and cures.

Discussions are currently underway on how to close the gap between the discovery and delivery of innovative products. With so much progress already achieved at the product review stage, more attention is being focused on early stage development and the clinical trials process. While changes are appropriate and important, none should lower FDA's evidentiary standards, otherwise patients would be exposed to unreasonable and unnecessary risks associated with insufficient information. The agency looks forward to continuing to work with others, including Congress, industry, academia, patients and advocacy groups, on these issues.