Targeted Drug Development:
Why Are Many Diseases Lagging Behind?

July 2015

U. S. Food and Drug Administration

FDA

Executive Summary

Through the efforts of Congress and the U.S. Food and Drug Administration, FDA's drug approval process has become the fastest in the world—and Americans have first access to new drugs more often than anywhere else in the world. While FDA has worked to transform the landscape for the final stage of drug development, progress in the discovery and testing stages of drug development has not kept pace. As a result, too many diseases are still awaiting treatments and cures.

More than a decade ago, FDA recognized that although scientists were mapping the human genome and making revolutionary discoveries in basic science, translating these discoveries into treatments had not kept pace. In response, FDA has for many years been building collaborations with industry and academia to modernize the "translational" science of drug development. FDA's goal is to improve the efficiency and predictability of clinical drug development through the development and use of such tools as genomic data, biomarkers and surrogate endpoints, modernized clinical trial designs, disease modeling and clinical trial simulation (bioinformatics), and advanced imaging technology. These tools have the potential to dramatically reduce the length and cost of drug development, for example, by predicting drug efficacy and toxicity earlier and avoiding wasteful late-stage failures. In addition, these tools can help target drugs to specific patient populations who can benefit most without facing unacceptable side effects, thereby limiting the number and size of clinical trials.

The speed with which the scientific community can develop and use these tools to shorten drug development in particular disease areas is highly variable. For example, the ability to use genetic data to identify useful biomarkers and surrogate endpoints in a specific disease is dependent on how well we understand the molecular and genetic bases for the disease. In some disease areas, we have made tremendous progress in our understanding of the causes of the disease and the interventions that can treat or cure it. FDA's success in getting effective drugs for cancer, HIV/AIDS, and other viral infections to market quickly has been widely noted. This achievement is based on decades of intensive research on cancer and HIV/AIDS that has given us critical insights into the pathways through which these (and related) diseases can be attacked. Such research has also led to the discovery of biomarkers that have provided insight on the genetic and metabolic characteristics that alter patients' responsiveness to particular drugs, and predict whether drug candidates are likely to work. This knowledge has resulted in important breakthroughs, rapid drug development, and a robust pipeline of new therapies for these particular diseases.

For other diseases, however, like Alzheimer's, we still lack basic information about the causes of the disease and the pathways for slowing its progress. As a result, we have witnessed a series of failed attempts to find biomarkers or surrogate endpoints that can predict disease progression or drug activity, and available treatments are limited.

In the middle are many other diseases such as diabetes. For these diseases, our understanding of disease causation and progression is sufficient to permit our use of certain tools such as surrogate endpoints. But it is insufficient to develop others such as biomarkers to help target specific subset of patients who are less likely to suffer side effects from specific drugs. Even where scientific research has not yet identified the molecular and genetic bases for a disease and its treatment, FDA is using tools other than targeting and biomarkers to reduce the length and cost of clinical trials, including flexible trial designs, expedited development pathways, public-private research collaborations, and intensive engagement with drug sponsors. In addition, these tools can support the development of one of the most promising avenues for accelerating drug development: targeted, or precision, medicine—the ability to target the right drug to the right patient based on understanding of the genetic and biochemical basis of a disease in patient subgroups.

This white paper briefly describes the state of scientific knowledge and its effect on drug development in four key disease areas other than cancer and HIV/AIDS. It begins with a look at Alzheimer's disease, where the science is still weak; continues through diabetes and some rare diseases, where the science is progressing; to hepatitis C, where, because of its similarities to HIV/AIDS, the science is robust. We also describe the tools FDA uses to reduce the length and cost of clinical trials in these disease areas, even where basic and translational science is lacking.

Alzheimer's Disease: Like many other diseases of the brain, Alzheimer's illustrates the obstacles to development of biomarkers and targeted drugs when scientific research has not yet uncovered the underlying causes or pathways of a disease. The National Institutes of Health (NIH) and others are funding promising research in this area. For all but rare genetic forms of the disease, however, scientists have not yet confirmed that any potential biomarkers can accurately identify individuals who have Alzheimer's, predict its clinical progression in specific patients, identify successful drug targets, or identify subsets of patients who might respond differently to different treatments. Thus far, promising biomarkers, when tested, have all failed to predict clinical improvement. For example, the hypothesis that amyloid plaque plays a key causative role in Alzheimer's led to the development of a series of drugs targeted at plaque formation. Unfortunately, when tested in patients with Alzheimer's symptoms, these drugs have failed to show any medical benefits. Although science has not yet demonstrated the ability of biomarkers to target therapies for Alzheimer's, FDA is helping to facilitate development of potential treatments for the disease by allowing surrogate endpoints to support product approvals, encouraging the use of enrichment designs in clinical trials, and collaborating with the healthcare community on the development of biomarkers.

Diabetes: Although the major factors associated with the development of diabetes are generally understood, the exact genetic, molecular, and environmental causes of both type 1 and type 2 diabetes remain to be discovered. Scientists do not yet understand the multiple genetic, immunologic, and metabolic differences among subsets of patients that would allow them to accurately predict which patients will develop diabetes, which patients will respond to specific drugs, or which patients will be susceptible to serious drug side effects. Without this information, it is not yet possible to develop drugs

targeted to prevent or treat diabetes in particular patients. And it remains necessary to test new diabetes drugs in a broader patient population.

Despite scientists' incomplete understanding of diabetes and its causes, FDA has long allowed manufacturers to show that a diabetes drug works by using a simple surrogate endpoint: lowered blood sugar. FDA also permits the use of biomarkers for "proof of concept" and establishing an appropriate dose, and it is participating in the development of other biomarkers. Because many drug sponsors, are small companies (particularly those working on type 1 diabetes), and the studies are challenging, FDA is working intensively with them to help them navigate the regulatory process and design flexible clinical trials. The diabetes drug pipeline is among the strongest for any disease category, and includes potentially transformative advances for type 1 diabetes.

Rare Diseases: Scientific understanding about the causes of rare diseases—those affecting fewer than 200,000 patients--varies by disease. For a small number of rare diseases, including some cancers and cystic fibrosis, scientific research has given scientists a good understanding of the disease and its genetic and molecular pathways. For many other rare diseases, however, basic research is lacking, which limits scientists' understanding of their causes or how to intervene in their progression. As a result, we lack drug targets and biomarkers that can be used to help make clinical trials more efficient and successful. Nevertheless, FDA is actively engaged in helping companies speed development of potential treatments for rare diseases by designing trials that address the challenges of small patient populations and novel endpoints. More than 95% of FDA-approved drugs for rare diseases benefitted from flexible clinical trial designs and expedited drug development programs. And between 50% and 60% of rare disease therapies were approved on the basis of surrogate endpoints.

Hepatitis C: For decades, hepatitis C infection was poorly understood and could be treated only with untargeted anti-viral drugs such as interferon, which cured only about 10% of patients and had severe toxicity. In the 1990s, however, the knowledge and technology developed in the massive research effort on the HIV/AIDS virus helped unravel the genetic and molecular bases for other viral infections. Since 2011, FDA has been approving targeted treatments for hepatitis C, and in December 2013, FDA approved the most dramatic improvement in therapy to date. The targeted drug Sovaldi provides a greater than 90% virologic cure rate in the hepatitis C genotypes for which it is approved, has manageable side effects, and does not require co-administration of interferon for most patients.

Targeted medicines offer the promise of breakthrough disease treatments and a shortened path from discovery to market. The scientific community has made great strides in developing targeted medicines and biomarkers for cancer and HIV/AIDS because we have made a substantial and sustained investment in research into these diseases over several decades. But inadequate scientific understanding of other diseases is likely to remain the most important limiting factor for developing targeted therapies in these other areas. To develop the treatments and cures that patients need, the healthcare community—including patient groups, government, industry, and researchers—must continue to work together to improve both our understanding of these diseases and the tools needed to translate scientific discoveries into cures.

Introduction

Congress and FDA have worked hard to make sure that the drug approval process—the final stage of drug development—provides Americans with the earliest possible access to safe and effective drugs. As a result, since 2001, FDA's approval process has become the fastest overall in the world, and Americans have had first access to new drugs more often than anywhere else in the world.[1] And, over the last 50 years, the growth of modern science has stimulated the development of drugs for a wide variety of diseases that were previously untreatable.

Yet, despite these successes at speeding up drug approval, as well as recent leaps forward in our understanding of human biology, too many diseases are still awaiting treatments and cures. Serious public health needs, such as treatments for Alzheimer's disease, are not being met. And rising research and development (R&D) expenditures are not being matched by a proportionate discovery of innovative medicines. There is broad agreement that the healthcare community must find ways to make the early stages of drug discovery and testing more productive and efficient. The mapping of the human genome and important discoveries in molecular biology have set the stage for one of the most promising avenues for accelerating drug development: targeted medicine (also called "precision medicine"), which refers to the ability to target the right drug to the right patient based on understanding of the genetic and biochemical basis of a disease in patient subgroups.

For some diseases, targeted medicines are becoming a reality. Targeted therapies have been successfully developed in cancer and HIV/AIDS and other viral infections, and FDA has been an active partner with industry in bringing these drugs to market swiftly. This has resulted in rapid drug development, important breakthroughs for patients, and a robust pipeline of new therapies for cancer and HIV/AIDS. Yet targeted medicines have not yet been developed for a host of other diseases.

Why has scientists' ability to develop targeted medicines been confined mostly to cancer and HIV/AIDS viral infections? Advances in targeted treatments of cancer and viral infections are the result of decades of investment in research by the National Institutes of Health (NIH) and others. And this research has produced a detailed understanding of the often complex genetic and biochemical causes, pathways, and progression of cancer and HIV/AIDS viral infections in affected subpopulations. As part of this scientific investment, researchers have also developed the tools and technology to translate this understanding into treatments, including identification of response biomarkers. These advances have propelled successful drug targeting to specific cancer and HIV pathways that has led to improved efficacy of drugs for many patients. The numbers reveal the extent of this success. Targeted therapies, primarily for

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

treatment of these diseases, have grown rapidly through the combined efforts of researchers, industry, and FDA: 45% of the novel drugs FDA approved in 2013 are targeted to specific patients, compared to 23% from 2010 through 2012 and 5% in the early 1990s.

The level of scientific evidence available to develop targeted medicines and identify biomarkers in many other diseases is far more limited, however. The great majority of diseases are highly complex, involving many genetic variants as well as biochemical and environmental causes (which are sometimes much more influential than genetic factors), with multiple variations in different subpopulations. Some diseases, like Alzheimer's and other diseases of the brain, as well as many rare diseases, are many years behind cancer and HIV/AIDS viral infections in scientific understanding. When scientists don't understand disease pathways, biochemical targets and biomarkers that appear to be linked to disease progression often fail because, while associated with the disease, they are not directly in the *causal* pathway for the disease. Drugs developed to attack these incidental targets turn out not to help patients, and sometimes to hurt them. The recent surprising phase 3 failures of several drugs intended to prevent heart attacks by raising HDL (the "good" cholesterol) illustrate the risk of relying on a biomarker that was widely accepted, yet unproven in clinical trials. Despite widespread belief in this target, raising HDL turned out in clinical trials not to prevent heart attacks—and in one case was associated with an increased risk of adverse cardiovascular events.[2] There are many other examples of promising targets and biomarkers that failed because researchers' understanding of disease pathways was inadequate.

What does this mean for major disease areas that lag far behind cancer and HIV/AIDS viral infections in scientific understanding? Unfortunately, we have witnessed a series of failed attempts to identify drug targets or biomarkers in these diseases. These experiences have made clear that targeted drug development cannot get ahead of the underlying science. The success of targeted treatments for cancer and HIV/AIDS viral infections has been the result of a sustained investment in research. Major progress in treating Alzheimer's and many other diseases will require similar resources to help close the gaps in basic and translational science. Collaborative efforts involving industry, government, patient groups, and academia will also be essential.

This white paper briefly describes the state of scientific knowledge and its effect on drug development in four key disease areas other than cancer and HIV/AIDS. It starts with Alzheimer's disease, where the science is still weak; continues through diabetes and some rare diseases where the science is progressing; and concludes with hepatitis C where, because of its similarities to HIV, the science is robust.

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[2] Keene D, Price C, Shun-Shin MJ, Francis DP. Effect on cardiovascular risk of high-density lipoprotein targeted treatments niacin, fibrates, and CETP inhibitors: meta-analysis of randomized, controlled trials including 117,411 patients. *BMJ* 2014; 349:4379.

The paper also describes the tools FDA uses to improve the efficiency of drug development in these diseases, even where basic and translational science is lacking. FDA is active in initiatives to modernize and speed the earlier stages of drug development, from collaborations to improve the science of biomarkers and surrogate endpoints to working closely with drug manufacturers, investigators, and patient groups on clinical trial design early in drug development, resulting in substantially shorter development times.

The tools FDA uses to reduce the length and cost of clinical trials include:

- Meeting frequently and working closely with industry sponsors well in advance of the submission of a marketing application, to plan efficient clinical trial programs—a process that has been shown to shorten drug development by several years;

- Using flexible clinical trial designs in almost half of all drug approvals and in 80% of orphan drug approvals;

- Issuing guidance on the use of "adaptive" trial designs that allow modifications in the design as information about response to the drug accumulates. This results in shorter, smaller trials that are more likely to demonstrate an effect,[3] and "enrichment" strategies to enroll patients who are more likely to demonstrate a response to a drug[4];

- Supporting the creation of clinical trial networks and "master protocols" to vastly reduce the cost of conducting clinical trials;

- Expediting the development and review process through a variety of review and approval pathways, including Fast Track designation, Breakthrough designation, Priority Review, and Accelerated Approval; and,

- Using surrogate endpoints when appropriate both in Accelerated Approvals and traditional approvals, including 60% of rare disease approvals.

State of Drug Discovery and Development

Alzheimer's Disease

Alzheimer's is a progressive, fatal form of dementia that causes memory loss, cognitive impairment, and behavioral problems. It affects more than 5 million Americans. The disease is devastating to patients and

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[3] FDA Draft Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics, Feb. 2010.

[4] FDA Draft Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products, Dec. 2012.

their families, including the very high cost of care, and is expected to triple in prevalence over the next three decades. Finding effective treatments is an urgent public health goal.

Like many other neurodegenerative diseases, including Parkinson's and amyotrophic lateral sclerosis (ALS), Alzheimer's illustrates the obstacles to drug development where basic scientific research has not yet uncovered the underlying causes or pathways of a disease, or how to intervene in the disease process. Our ability to image the brain is rudimentary—too coarse to capture its circuitry and too slow to monitor cognitive activity. We do not yet understand the complex processes that underlie brain function and do not have reliable biomarkers that could aid in the development of treatments to halt or reverse the progression of most neurodegenerative diseases.

Scientific understanding of the disease

How well do scientists understand the genetic and molecular basis of Alzheimer's? Scientific knowledge of Alzheimer's disease is still in its infancy. Like many other diseases of the brain—which according to NIH remain "one of the greatest mysteries in science and one of the greatest challenges in medicine"—scientists lack a basic understanding of the genetic, biochemical, and environmental causes of Alzheimer's. Despite years of research, the causes and key genetic and biochemical pathways of Alzheimer's remain largely unknown, except in a very rare subset of cases where a clear genetic association has been identified. The progression of the disease varies significantly from patient to patient for reasons that remain a mystery. There are no biomarkers or diagnostic tests that can be used to confirm conclusively that a patient has or will get Alzheimer's; diagnosis is confirmed by autopsy after death.

Without more basic scientific information about the causes and progression of the disease, drug companies must develop possible treatments based on guesses about how the disease develops and progresses. These guesses have borne costly failures. For example, brain autopsies of Alzheimer's patients reveal amyloid plaque build-up, protein "tangles," and inflammation in the brain, but the role of these abnormalities in the development of the disease is not yet understood. Attempts to target the development of these abnormalities to slow progression of the disease have led to a series of high-profile failures. For example, the hypothesis that amyloid plaque plays a key causative role in Alzheimer's has led to the development of a series of drugs targeted at plaque formation. Unfortunately, when tested in patients with Alzheimer's, these drugs have failed to show medical benefits.

Can scientists target drugs to prevent or treat Alzheimer's disease in specific patients or identify key biomarkers? No. Except for very rare cases of familial Alzheimer's, scientists have not yet found biomarkers that can accurately: (1) identify individuals who have the disease, (2) predict clinical progression, (3) identify successful drug targets, or (4) identify subsets of patients who might respond differently to different treatments. As a result, it remains necessary to test new drugs in a broad population. Thus far, promising biomarkers, when tested in patients' with Alzheimer's symptoms, have failed to predict clinical improvement. And some tested drugs have exposed patients to unexpected and

serious toxicity in clinical trials, underscoring the difficulty in predicting clinical response based on the existing state of knowledge.

NIH and others are funding promising research in this area. For example, researchers have identified biomarkers that indicate a higher risk for developing Alzheimer's, though these biomarkers cannot determine whether a patient actually has or definitely will get Alzheimer's. And research is being funded by NIH in patients who have early brain changes revealed on brain scans and who may be at risk for Alzheimer's. The research will determine if certain drugs that target amyloid plaque may be effective when given before symptoms develop.

What research is needed to allow scientists to target drugs in patients with Alzheimer's disease? Much additional research is needed to understand the causes of Alzheimer's, including basic research on the workings of the brain, the genetic and environmental factors that influence the development and progression of the disease in affected subpopulations, and improved imaging technology and biomarkers for diagnosing the disease and assessing the impact of interventions. According to NIH, "significant breakthroughs in how we treat neurological and psychiatric disease will require a new generation of tools to enable researchers to record signals from brain cells in much greater numbers and at even faster speeds." [5] NIH recently announced BRAIN (Brain Research through Advancing Innovative Neurotechnologies), a 12-year, $4.5 billion research initiative to develop those tools.

FDA actions to accelerate Alzheimer's drug development

Although the science does not yet exist to identify biomarkers to support targeted therapies for Alzheimer's, FDA is helping to facilitate development of potential treatments for the disease, including reliance on surrogate endpoints to support product approvals, encouraging the use of enrichment designs in clinical trials, and collaboration on the development of biomarkers.

Use of surrogate and intermediate endpoints. To test Alzheimer's drugs in patients who have already developed dementia, FDA encourages companies to use two short-term clinical endpoints—cognitive and functional impairment—rather than long term disease-progression. Both are recommended because improvements on cognitive tests do not always signal improved functioning. Most drug development is focused on patients who have *not* yet developed dementia, in the hope of halting the disease before it causes substantial damage. In those patients, showing an effect on functional impairment is challenging because the impairment is so mild. Accordingly, FDA has indicated its willingness to use Accelerated Approval, allowing companies to rely only on a more easily demonstrated

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[5] National Institutes of Health, Why Is The BRAIN Initiative Needed? http://www.braininitiative.nih.gov/why.htm

short-term clinical endpoint—cognitive improvement or stabilization—if there is clear evidence of an effect on a valid and reliable cognitive assessment.[6]

Working with companies. FDA works closely with companies developing Alzheimer's drugs to develop flexible trial designs and more easily interpretable endpoints and, for small companies with less experience, to help them move efficiently through the regulatory process.

Use of unqualified biomarkers for enriched trial designs. To increase the chance that a clinical trial will correctly identify an effective drug in early-stage Alzheimer's, FDA encourages drug sponsors to "enrich" the study population with patients most likely to progress to overt dementia. FDA allows companies to use possible biomarkers, such as amyloid plaque imaging, brain image region measurement, and protein in cerebrospinal fluid as aids to enriching clinical studies with patients who may improve the ability to show the effectiveness of the drug.

Biomarker development. FDA scientists are collaborating with groups including the Alzheimer's Disease Neuroimaging Initiative and the Coalition Against Major Diseases (within the Critical Path Institute) to find biomarkers that can (1) identify Alzheimer's patients before they show symptoms; (2) distinguish among those whose disease will progress more slowly or more quickly; and (3) predict the clinical outcomes of interventions.

Recent approvals and drugs in the pipeline

The only drugs approved for Alzheimer's disease provide limited improvement of cognitive symptoms, and the last was approved in 2003. A number of drugs that are hoped to slow disease progression, based on various hypotheses about the causes of the disease, are in the pipeline.

Diabetes

In patients with diabetes, the pancreas stops making sufficient quantities of insulin to control the amount of sugar in the blood, or the body becomes resistant to insulin, or both. As a result, blood sugar becomes elevated. Over time, uncontrolled blood sugar can lead to major health problems, including heart attack, stroke, kidney disease, amputation of toes or feet, and blindness. There are two main types of diabetes: type 1 (5% of cases) and type 2 (more than 90% of cases). Type 1 diabetes (formerly known as juvenile diabetes) usually begins in childhood or adolescence and is an auto-immune disease: The immune system attacks the cells that produce insulin and patients become completely dependent on insulin injections. Type 2 diabetes, in which the pancreas produces some insulin but the body can't use it well, typically begins in adulthood, but is increasingly diagnosed in younger people, mainly as a result of

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[6] FDA, Draft Guidance, Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease. Feb. 2013. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM338287.pdf.

childhood obesity. As obesity rates rise, we are facing a dramatic increase of diabetes in this country and worldwide, heightening the need for effective, safe new treatments.

Scientific understanding of the disease

How well do scientists understand the genetic and molecular basis of diabetes? Although the major abnormalities that lead to the development of diabetes are generally understood, the exact genetic, molecular, and even environmental causes of type 1 and type 2 diabetes remain to be discovered. Research has identified some of the genes that influence the onset of diabetes, but multiple genes are thought to play a role, and the influence of each single gene on disease causation is thought to be small. Type 2 diabetes tends to run in families, and there continues to be extensive research aimed at identifying specific susceptibility genes. However, with rare exceptions, scientists have not yet discovered specific genetic markers that are capable of predicting risk of type 2 diabetes.

In addition, diabetes patients vary in their rate of progression, in the signs and symptoms of their disease, and in responses to treatment—but for many patients we do not yet understand why. Triggers other than genes, such as diet, infection, certain metabolic disorders, obesity, and some drugs can also be involved and likely interact with an individual's genetic susceptibilities.

Nevertheless, there have been great advances in identifying genetic and immune biomarkers of susceptibility for type 1 diabetes. Although we do not yet have biomarkers that can predict response to treatment, we are nearing the point at which these biomarkers will be able to predict at-risk patients (usually children or adolescents) for the more limited purpose of deciding which patients may qualify for clinical trials of new drugs and biologics aimed at prevention.

Can scientists target drugs to prevent or treat diabetes in specific patients? No. Specific genetic defects and abnormalities in patients with type 1 and type 2 diabetes and abnormalities in the regulation of the immune system in type 1 diabetes have been identified. But scientists do not yet understand the multiple genetic, immunologic, and metabolic differences among subsets of patients that would allow them to accurately predict which patients will develop diabetes, which diabetics will respond to specific drugs, the degree of beta cell reserve (for type 2 diabetics) or which patients will be susceptible to serious drug side effects. Without this information, it is not yet possible to develop drugs targeted to prevent or treat diabetes in particular patients and it remains necessary to test new diabetes drugs in a broader patient population. The major goal of therapy is to normalize blood sugar levels and thereby reduce the risk of short and long-term complications.

What research is needed to allow us to target drugs in diabetes? More basic research is needed to increase scientists' understanding of the interaction between genetic, immunologic, metabolic, and environmental factors that cause specific subsets of patients to develop the disease and why the progress, signs, and symptoms of the disease are variable from patient to patient. Scientists still need to understand much more about why and how the immune system attacks the pancreas, to allow development of treatments that target the specific auto-immune process rather than suppressing the

entire immune system, which carries serious risks. Further research is also needed to find biomarkers for susceptibility to specific complications of diabetes (as opposed to the disease itself).

FDA actions to accelerate diabetes drug development

Use of surrogate endpoints. Despite the incomplete understanding of diabetes and its causes, FDA has long allowed manufacturers to show that a diabetes drug works by using a simple surrogate endpoint—lowering blood sugar. FDA does not require long, expensive clinical trials showing that a drug reduces the long-term health problems caused by diabetes, such as heart disease and limb amputations. In fact, no drug for type 2 diabetes has ever been approved based on demonstrating effectiveness in preventing these complications. There have been longstanding concerns that some drugs for type 2 diabetes that successfully lower blood sugar may nevertheless increase rather than decrease the risk of heart attack. This has resulted in external calls to stop approving diabetes drugs on the basis of a surrogate endpoint.

FDA continues to believe that lowering blood sugar levels is a valid surrogate for diabetes drug efficacy. FDA also recognizes the public health concerns raised by drugs to treat diabetes in a large and growing population of people with diabetes if such drugs have the potential to cause a significant increase in the risk of heart attacks. (More than 20 million people have been diagnosed with diabetes in the United States.) Because biomarkers are not available to identify patients at greater risk of drug-related heart attacks or strokes, FDA issued a guidance in 2008 recommending testing of the effect of new diabetes drugs on the cardiovascular (CV) system. To minimize the impact on innovation while ensuring acceptable cardiovascular safety, FDA asks for preliminary CV safety data before approval and for detailed additional data to characterize CV effects after the product is on the market.

Use and development of biomarkers. Because patients in early clinical trials of type 1 diabetes drugs may be receiving insulin via an insulin pump, it is difficult to determine how much insulin their own pancreas is secreting. In such cases, FDA allows use of a biomarker of insulin secretion, known as C-peptide, which is secreted along with insulin. C-peptide is universally recognized as a marker of insulin production though it has no established major role in metabolic control and FDA permits its use to establish "proof-of- concept" and to select an appropriate dose. FDA is also participating in the development of biomarkers for measuring the function of insulin-producing cells in type 2 diabetes, through the Biomarker Consortium managed by the Foundation for the National Institutes of Health. Researchers hope this will lead to improved techniques for tracking progression of the disease, stratifying patients by severity for entry into clinical trials, and developing more effective treatments. Research is also ongoing to find biomarkers for susceptibility to specific complications of diabetes.

Working with drug sponsors. Because many drug sponsors (particularly those working on type 1 diabetes) are small companies, and because studying the interventions is challenging, FDA is working intensively with them to help them navigate the regulatory process and design clinical trials.

Designing efficient, flexible clinical trials. FDA scientists are working closely with drug sponsors (particularly small companies and academic investigators) to design clinical trials of promising experimental treatments for type 1 diabetes, including transplantation of insulin-producing islet cells to

replace cells destroyed by the immune system. In clinical trials of the effectiveness of allogeneic islets, a randomized, concurrent-control trial design may not be feasible or even necessary. FDA noted emerging data from phase 2 trials showing that the effects of islet cell transplantation (i.e., insulin independence, prolonged absence of hypoglycemic events, ease of blood sugar control with small amounts of insulin in subjects who still required some insulin) virtually never occur in type 1 diabetes spontaneously, that is without treatment. Based on these considerations, FDA issued a guidance[7] stating that a single-arm, open label trial without a concurrent control group may be able to provide adequate evidence of effectiveness of allogeneic islet cells. This guidance also identified endpoints that could be used in such trials. Using these principles, FDA worked with NIH in designing phase 3 islet transplantation trials that are currently being conducted by a consortium of investigators and funded by NIH.

FDA is also helping sponsors develop flexible trial designs for other innovative therapies for type 1 diabetes, including stem cell therapy and therapy to interfere with the auto-immune process that destroys the body's ability to make insulin. FDA also participates in a multidisciplinary group of scientists, in partnership with NIH, to help accelerate the development of the "artificial pancreas." This effort has resulted in an FDA guidance, and clinical trials of an artificial pancreas are underway.

Recent approvals and therapies in the pipeline

FDA has approved seven new diabetes drugs in the last two years. This includes three drugs that represent entirely new drug classes—a measure of how innovative these drugs are. In June 2014, FDA approved the only inhaled insulin product. The diabetes drug pipeline is among the strongest for any disease category and includes potentially transformative advances for type 1 diabetes.

Rare Diseases

Rare or "orphan" diseases are defined as diseases that affect fewer than 200,000 patients in the United States. Most rare diseases are serious or life-threatening and patients have unmet medical needs. Since passage of the Orphan Drug Act of 1983, which provided economic incentives for drug development, the number of orphan drug designations and approvals has surged. The number of orphan drug designations has more than doubled in the last seven years, to 440 in 2014. Many rare diseases remain in need of treatments, however. FDA is actively engaged in helping companies speed development of potential treatments for rare diseases, including frequent reliance on surrogate endpoints and flexible clinical trial designs.

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[7] FDA, Guidance for Industry: Considerations for Allogeneic Pancreatic Islet Cell Products, Sept. 2009 http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgen etherapy/ucm182440.htm.

Scientific understanding of rare diseases

How well do scientists understand the genetic and molecular basis of rare diseases? Scientific understanding about the causes of rare diseases varies by disease. For a small number of rare diseases, including some rare cancers, cystic fibrosis (CF), and phenylketonuria (PKU), scientific research has given us a good understanding of the disease and its genetic and molecular pathways. For far more rare diseases, however, basic research is lacking, limiting our understanding of their causes, their natural histories, or how to intervene in their progression. As a result, we do not yet have biomarkers and drug targets that can be used to help make clinical trials more efficient and successful.

Can scientists target drugs to prevent or treat rare diseases in specific patients? Yes, in some cases. Targeted drugs accounted for 60% of orphan drug approvals in 2013, compared to 20% of non-orphan approvals. For example, Kalydeco, the recently approved, groundbreaking treatment for a rare form of CF, targeted a specific genetic mutation in a subset of CF patients. It is the first drug treatment to target one of the genetic causes of CF rather than its symptoms and provides dramatic, sustained improvement in lung function. For the majority of rare diseases, however, scientific knowledge is far from where it needs to be to develop targeted drugs or biomarkers that can predict clinical outcomes.

What research is needed to allow us to target drugs for more rare diseases? For the great majority of rare diseases, much more research is needed into the genetic, biochemical, and environmental causes of the diseases, their natural history, and the biomarkers that can diagnose patients and assess the effects of drug treatment.

FDA actions to accelerate drug development for rare diseases

More than 95% of drugs approved for rare diseases benefitted from flexible clinical trial designs and expedited drug development programs.

Use of surrogate endpoints. Fifty percent to 60% of orphan drug approvals are based on surrogate endpoints, using the Accelerated Approval or traditional approval pathways, depending on whether the surrogate endpoint has been validated (confirmed to predict clinical outcome). When the surrogate endpoint is validated and therefore adequate to support a traditional approval, the company need only show an effect on the surrogate and is not required to reconfirm the clinical benefit of the drug after approval.

Working with companies. FDA works very closely with orphan drug developers to design trials that address the challenges of small patient populations and novel endpoints, as well as ethical issues raised by testing experimental drugs in young children. FDA knows that the small patient populations generally mean that research data will be limited and encourages companies to meet early in development to design highly efficient trials. Eighty percent of orphan drugs also qualify for one or more of FDA's expedited development programs, including Breakthrough Therapy designation, which involves close collaboration with FDA on product development.

Flexible trial designs. Customized, flexible trial designs are used in 80% of rare disease approvals.[8] Almost two-thirds of orphan drugs are approved on the basis of a single clinical trial, rather than the traditional standard of two randomized, controlled trials. Some of these trials use historical information about untreated patients as a "control" group, rather than a concurrent control group receiving a placebo or an "active control" treatment if there is one. Novel endpoints (those never before accepted for any drug) are used in 25% of rare disease studies. FDA is also encouraging the development of clinical trial networks for rare diseases to avoid the need to recreate clinical trial infrastructures for each new clinical trial, sparing limited resources and encouraging patient participation.

Collaborations. FDA is collaborating with NIH, industry, academia, and patient groups to develop new information about rare diseases, biomarkers, and outcome measures for clinical trials. For example, FDA is collaborating with the National Organization for Rare Disorders (NORD) to develop natural histories of specific diseases to understand their progression. FDA also holds or participates in many scientific meetings and workshops to advance the state of knowledge about rare diseases and understand their unmet needs. FDA also participates in many forums to educate and inform stakeholders about regulatory requirements and approaches.

Recent approvals and drugs in the pipeline

Orphan drugs account for a third of all novel drug and biologic approvals. Recent orphan drug approvals include first-time-ever disease-modifying treatments for CF, several rare cancers, rare genetic diseases, and multi-drug resistant tuberculosis. In most cases, scientific understanding of these diseases has benefitted from successful research on related diseases. The pipeline for orphan drugs is robust in many disease areas, and investment in orphan drug development has risen substantially.

Hepatitis C

Hepatitis C is a liver disease caused by infection with the hepatitis C virus, which can lead to cirrhosis, liver cancer, or liver failure. It is the most common reason for liver transplants in the United States and now kills more Americans than HIV. About 3.2 million Americans (and about 150 million people worldwide) are infected with hepatitis C. Recent revolutionary breakthroughs in hepatitis C treatment illustrate both the promise of targeted drugs and the scientific foundation that catalyzes investment and makes targeted drug development possible.

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[8] Frank J. Sasinowski, National Organization for Rare Disorders, Quantum of Effectiveness Evidence in FDA's Approval of Orphan *Drugs: Cataloguing FDA's Flexibility in Regulating Therapies for Persons with Rare Disorders.* Released October 11, 2011.
http://nordphysicianguides.org/wp-content/uploads/2012/02/NORD-study-of-FDA-approval-of-orphan-drugs.pdf

Scientific understanding of hepatitis C

How well do scientists understand the genetic and molecular basis of hepatitis C? For decades hepatitis C infection was poorly understood and could be treated only with untargeted anti-viral drugs like interferon, which cured only about 10% of patients and had severe toxicity. In the 1990s, however, the knowledge and technology developed in the massive research effort on the AIDS virus helped unravel the genetic and molecular bases for other viral infections. Technology developed in 1999 permitted scientists to screen drug candidates by measuring the growth of hepatitis C-infected cells in a test tube. Very quickly, many promising "direct-acting" targeted drug candidates emerged. By the mid-2000s, these drugs were in clinical trials. And by 2011, FDA was approving targeted treatments with significantly improved cure rates and shorter treatment periods. But the first targeted anti-hepatitis C drugs still had to be used with interferon. In December 2013, FDA approved the most dramatic improvement in therapy to date: the targeted drug Sovaldi provides a greater than 90% virologic cure rate in the hepatitis C genotypes for which it is approved. Sovaldi is now being studied for use in other genotypes and is showing virologic cure rates of about 95%. Additional highly effective targeted drugs have quickly followed.

Can scientists target drugs to prevent or treat hepatitis C in specific patients? Yes. Scientific discoveries made in the intensive research effort on HIV/AIDS provided the foundation for understanding the hepatitis C virus and the proteins that could be targeted to prevent viral replication in specific patients.

FDA actions to accelerate drug development

Use of surrogate endpoints. FDA uses a surrogate endpoint called "sustained virologic response"—lack of detection of the virus in the blood 12 weeks after completing treatment—as the basis for drug approval, rather than a long-term clinical endpoint like survival or progression of liver disease.

Working with companies and flexible trial designs. FDA scientists were intensely engaged with companies in the development of the breakthrough hepatitis C drugs, providing guidance for trial designs that facilitated quick enrollment, analyzing data that allowed for a shorter primary endpoint assessment (12 weeks post-treatment instead of 24 weeks), and allowing the submission and review of late-breaking data during New Drug Application (NDA) reviews. FDA has also issued a draft guidance to assist companies in efficient development of targeted hepatitis C drugs.[9] The guidance recommends, when appropriate, conducting clinical trials with historical controls (use of pre-existing information on the course of the disease in past patients who received interferon) so that no current patients are put in an interferon control group. This promotes enrollment of patients intolerant of interferon or unable or unwilling to take interferon.

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[9] FDA, Draft Guidance for Industry, Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment. Oct. 2013.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225333.pdf.

Collaborations. FDA is collaborating with industry, academia and patient groups to assess impediments to hepatitis C drug developments, facilitate drug development, and provide data for labeling to inform physicians how to best use many potential hepatitis C drug combinations.

Recent approvals and drugs in the pipeline

FDA has approved targeted hepatitis C drugs that vastly increase virologic cure rates since May 2011. The hepatitis C drug pipeline is robust, with many promising new treatments under study.

Conclusion

Over the past generation, FDA has dedicated itself to assuring that the drug approval process—the final stage of drug development—provides Americans with the earliest possible access to safe and effective drugs. Drug review times have been slashed from years to months without compromising FDA's standard for approval. Today, the United States leads the world in the introduction of novel drugs, and Americans have first access to new treatments and cures.[10]

While FDA has transformed the final stage of drug development, the length and cost of the earlier discovery and testing stages must be improved. Overall pharmaceutical productivity has fallen: The cost of getting a drug from discovery to submission of a marketing application to FDA has escalated, and failure rates have grown. Targeted (or precision) medicines offer the promise of breakthrough disease treatments and a shortened path from discovery to market. Scientists have made great strides in developing targeted medicines and biomarkers for cancer and HIV/AIDS because there has been a substantial and sustained investment in research into these diseases over several decades. But inadequate scientific understanding of specific diseases is likely to remain the most important limiting factor for developing targeted therapies in other areas.

Even where scientific research has not yet identified the molecular and genetic bases for a disease and its treatment, FDA is using many scientific and regulatory tools to reduce the length and cost of clinical trials. FDA is active in initiatives to modernize and speed the earlier stages of drug development, from collaborations to improve the science of biomarkers and surrogate endpoints to working closely with drug manufacturers and patient groups on clinical trial design early in drug development, resulting in substantially shorter development times. But to develop the treatments and cures that patients need, the healthcare community, including patient groups, government, industry, and researchers, must continue to work together to improve both our understanding of disease and the tools to translate scientific discoveries into cures.

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