Continuing America's Leadership: The Future of Medical Innovation for Patients

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Health, Education, Labor and Pensions
United States Senate

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U.S. Department of Health and Human Services
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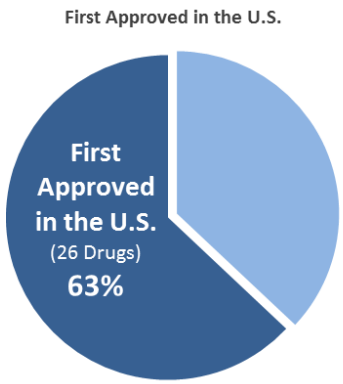
Center for Drug Evaluation and Research
www.fda.gov/drugs

Mr. Chairman and Members of the Committee, I am Dr. Janet Woodcock, Director of the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER). I am privileged to have the responsibility to oversee much of FDA's efforts to review the safety and efficacy of new pharmaceuticals. Thank you for having me here today to give you my views on current efforts and areas for improvement.

When I came to FDA in the 1980s, the process by which FDA approved new drugs for marketing to patients was under considerable criticism–for being slow, for lagging behind other countries, and for lacking transparency to, and collaboration with, the developers of new drugs.

Today, thanks to the efforts of those across the Agency, our nation's drug review process reveals a very different picture–we are delivering new, lifesaving therapies to patients faster than any other developed country and more expeditiously than ever before. In 2014, almost two-thirds of the novel ("new molecular entity") drugs approved by CDER (26 of 41, 63 percent) were approved in the United States before receiving approval in any other country. In addition, we have significantly strengthened the drug safety surveillance system in the United States, modernized drug review processes, and introduced new genomic and related sciences into the drug evaluation process.



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Factors Speeding Drug Review and Development

No single action or programmatic change has brought us to where we are today; rather, it has been a steady program of improvements, new investments through PDUFA, new authorities and other factors. These improvements were based upon both externally and

internally identified gaps, so that now we have more predictable review times, additional FDA resources to adequately address the workload from applications, and additional interaction between FDA staff and drug manufacturers to ensure promising drugs reach patients quickly.

Prescription Drug User Fee Program

The approval by this Committee of the Prescription Drug User Fee Act of 1992 (PDUFA) has been one of the most important components of our improvements in review times. As its name suggests, PDUFA provided funds in the form of user fees for FDA to hire sufficient staff to undertake the growing workload of applications to market new drugs in the United States. But it had much broader implications. It established the principle that timely review was important, not just to manufacturers, but also to patients, and that FDA should commit to conducting those reviews in a predictable manner.

I became Director of CDER not long after PDUFA's enactment and was determined from the start to ensure that the program was run in a business-like fashion, with use of modern project management techniques, establishment of specific goals, and accountability on the part of review staff and managers to adhere to those goals. The result has been a concerted effort across the Center with steady lowering of review times, greater predictability for industry, and most importantly, faster patient access to new therapies.

So, I thank the Committee for the user fee program. It has helped revolutionize our nation's drug review process speeding access to new drugs and without compromising the Agency's high standards for product safety, efficacy, and quality. In 2014, CDER met its PDUFA goal dates for 98 percent of the novel drugs we approved (40 of 41).

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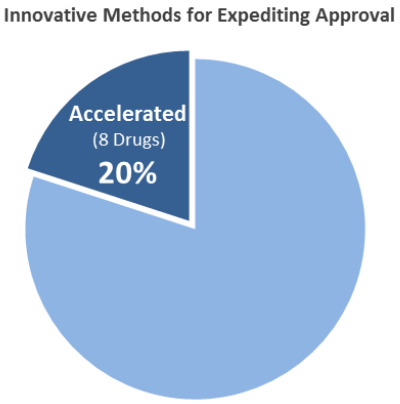
In addition to PDUFA, there have been a number of other important initiatives that have contributed to our progress in achieving these goals, including expedited FDA review programs, greater collaboration with industry, and the use of surrogate endpoints to advance drug development.

Expedited FDA Review Programs

FDA's expedited review programs were established in recognition of the need to find ways for therapies intended for serious conditions in patients with unmet medical needs to get into the hands of patients and health professionals more quickly.

Accelerated Approval

Around the time of PDUFA's passage, FDA created an "Accelerated Approval" program to permit certain drugs intended to treat serious and life-threatening medical conditions to be approved on the basis of a "surrogate endpoint"–that is, using a biomarker or measure that is "reasonably likely" to predict clinical benefit instead of directly measuring benefits to patients. As a condition of accelerated approval, sponsors must conduct or complete required post-approval studies to confirm that the drug actually helps people. Surrogate endpoints serve as stand-ins for clinical endpoints that measure the real benefits of drugs: whether a patient actually feels better or can function better, or lives longer. Surrogate endpoints generally allow clinical studies to be conducted in smaller populations of individuals over shorter periods of time, reducing both the time and cost of drug development. More information about how surrogate endpoints and other biomarkers are being used to advance drug development is included below.

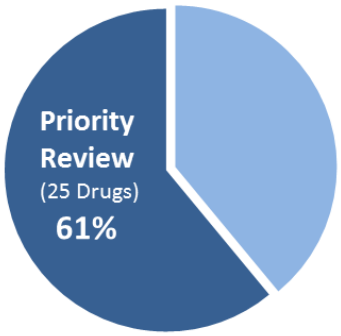


CDER approved eight of the 41 novel drugs approved in 2014 (20%) under FDA's Accelerated Approval program.

CDER has approved over 90 new drug and biologics applications more rapidly because of the Accelerated Approval program. In 2014, CDER approved eight of the 41 novel drugs approved (20 percent) under FDA's Accelerated Approval program.

Priority Review

Drugs with the potential to deliver a significant improvement in safety or effectiveness over existing therapy for serious or life-threatening illnesses may also be designated for "priority review." Priority review drugs receive a shortened, six-month FDA review goal. For example, from the beginning of 2008 through the end of 2014, 93 novel drugs and biologics approved by CDER received the shortened, six-month review dictated by priority-review designation. In 2014, 25 of the 41 novel drugs approved by CDER were designated Priority Review.



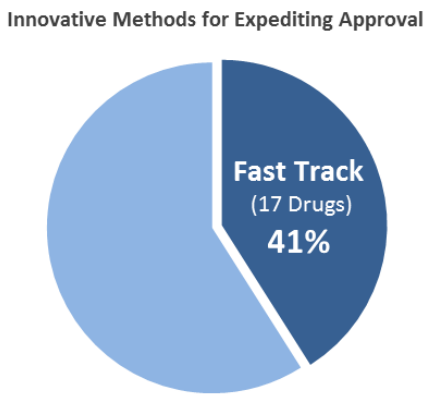
In 2014, 25 of the 41 novel drugs approved by CDER were designated Priority Review.

Fast Track

Another expedited program that helps reduce the time to market for drugs being developed for serious and life-threatening illnesses is known as "fast track." Fast-Track designation generally may be used for drugs intended to treat a serious condition where nonclinical or clinical data demonstrate the drug's potential to address an unmet medical need.

When a drug receives Fast-Track designation, FDA works closely with its sponsor to facilitate submission of the drug development plan, the design of clinical trials, and to identify any other data necessary to support FDA approval of the drug. Moreover, once the sponsor begins to develop the data to support approval, it can submit that data for "rolling review." Rolling review allows a sponsor to submit portions of a marketing

application in advance of the entire application, rather than submitting all portions of the marketing application at once, which is the usual process.



Seventeen of the 41 novel drugs (41%) approved by CDER in 2014 were designated as Fast Track.

Seventy-six novel drugs and biologics were approved by CDER from 2008 to 2014 with Fast-Track designation. Seventeen of the 41 novel drugs (41 percent) approved by CDER in 2014 were designated as Fast Track.

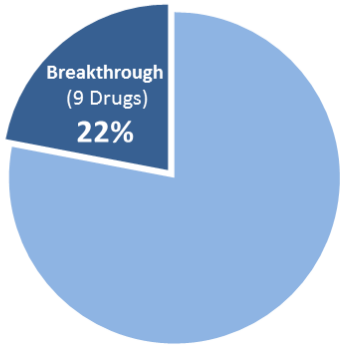
Breakthrough Therapy Designation

In 2012, Congress provided the "Breakthrough Therapy" designation as another new tool for expediting important new advances in therapy for serious and life-threatening illnesses.

Breakthrough therapy designation may be granted for a drug that is intended to treat a serious condition, where preliminary clinical evidence (i.e., in people) indicates that the drug may demonstrate substantial improvement on one or more clinically significant endpoints over available therapies. Such breakthrough therapies, like drugs that receive Fast-Track designation, receive intensive guidance from FDA, to help sponsors better tailor their drug development program and, thus, maximize the prospects for a rapid and successful path to approval. In addition, breakthrough therapy drugs receive an organizational commitment from FDA's senior managers and experienced review staff to collaborate in advancing the review of these potentially high-impact drugs.

As of April 16, 2015, CDER and the Center for Biologics Evaluation and Research (CBER) have designated more than 84 new therapies as breakthrough therapies, and 24 have received marketing approval. Moreover, initial experience with the breakthrough process has yielded more rapid FDA review times in many cases and

shortened overall development times for these therapies. Continued success of the breakthrough therapy drug program is expected as a result of FDA's intensive collaboration with new drug sponsors. CDER designated nine of the 41 novel drugs (22 percent) approved by the Center in 2014 as breakthrough therapies.



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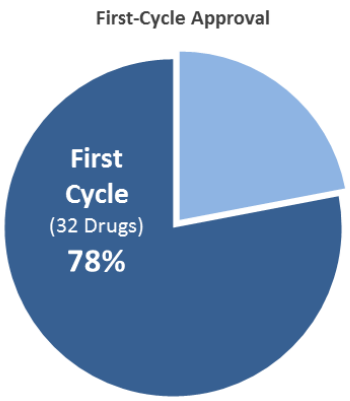
Greater Collaboration with Industry

The movement toward greater collaboration between industry and FDA, embodied in such initiatives as the Breakthrough Therapy program, is reflected throughout our efforts and is one of the more significant changes that has occurred during my time at FDA. In recent years, meetings between FDA and industry have become routine and have proven to be invaluable in improving communication about planned clinical trials, development milestones, and data requirements.

Average clinical development time was more than three years faster, when a pre-IND meeting was held.

The impact of improved FDA/industry communication is becoming increasingly evident. Recently, FDA took a look at the development times of new drugs that were approved with the benefit of pre-Investigational New Drug (IND) meetings and compared them to the development times for drugs that were approved without such meetings. The results were quite remarkable. For instance, for all new drugs approved between 2010 and 2012, the average clinical development time was more than three years faster when a pre-IND meeting was held, than it was for drugs approved without a pre-IND meeting. A 2014 article in *The Lancet*, "Biomedical research: increasing value, reducing waste" (January 11, 2014), noted that 85 percent, or $200 billion, of annual

global spending on research is wasted on badly designed studies, and I believe that greater industry-FDA collaboration can significantly reduce such wasted effort.



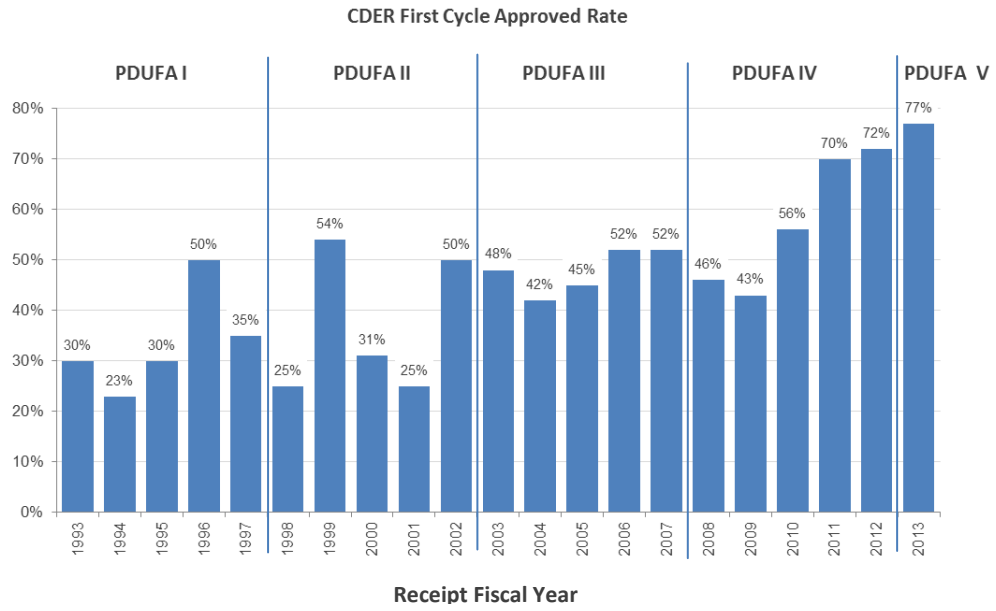
CDER approved most of the novel drugs of 2014 (32 of 41, 78%) on the "first cycle" of review.

Another result of improved collaboration between industry and FDA is a substantial reduction in the number of application review "cycles." The phenomenon of "multiple review cycles" occurs when a sponsor submits a marketing application for approval and FDA does not approve the drug during the first-review cycle. The most efficient outcome for both the Agency and industry is for an application to receive approval on the first-review cycle, if the drug is ultimately approvable. Not receiving FDA approval on the first cycle means that the sponsor must go back and take steps to collect additional data or address a deficiency in their marketing application and then resubmit their application, which FDA must then review again. But achieving first-cycle approval requires a well-prepared application with no major deficiencies.

As a result of better collaboration between industry and FDA… first cycle approvals… are now exceeding 70%.

As a result of better collaboration between industry and FDA, which has helped companies identify the data and analyses needed for approval before the application is submitted, first-cycle approvals, which until recently occurred for fewer than half of all novel drug submissions, are now exceeding 70 percent. For example, CDER approved 78 percent of the 41 novel drugs it approved in 2014 on the first cycle. This translates into reduced costs for industry and earlier patient access to new therapies, as illustrated by the charts. The early and frequent communications that characterize some of the expedited development programs were not possible before user fees were established, so, once

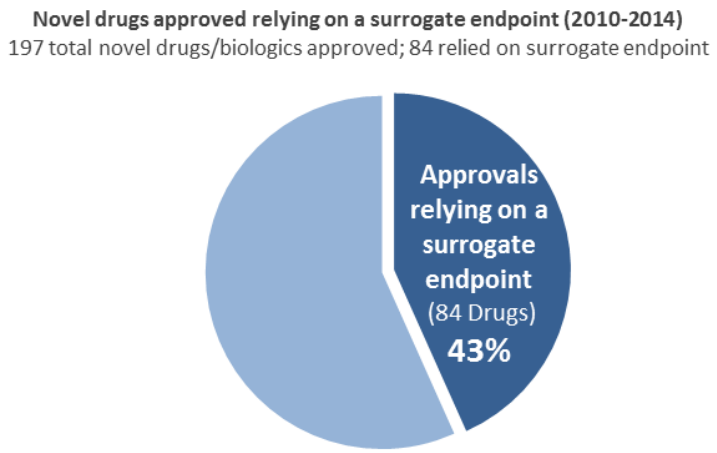
again, I commend this Committee for the authorization–and reauthorization–of the user fee program.



Using Surrogate Endpoints to Advance Drug Development

As noted above, FDA routinely permits the use of surrogate endpoints as the basis for Accelerated Approvals, when the surrogate is reasonably likely to predict clinical benefit in a serious or life-threatening disease that lacks good therapies. However, when scientific study has progressed sufficiently to establish the correlation between the surrogate endpoint and clinical benefit, the surrogate endpoint then may be relied upon as the basis for traditional approval, thereby negating the need for the confirmatory studies requirement, to which drug sponsors are subject, under Accelerated Approval. For example, reducing elevated blood pressure levels is a well-known surrogate endpoint to reflect reduction in cardiovascular outcomes such as stroke. Over many years, FDA has allowed the traditional approval pathway to be used in approving a wide range of blood pressure medicines, thereby dramatically expanding options for fighting stroke and other related cardiovascular conditions.

During the last five years (2010-2014), out of a total of 197 novel drugs and original biologics approved across FDA, 84 (43 percent) relied upon a surrogate endpoint for approval. A table listing the surrogate endpoints relied upon for these 84 approval determinations (covering both traditional approvals and accelerated approvals) is attached as an appendix.

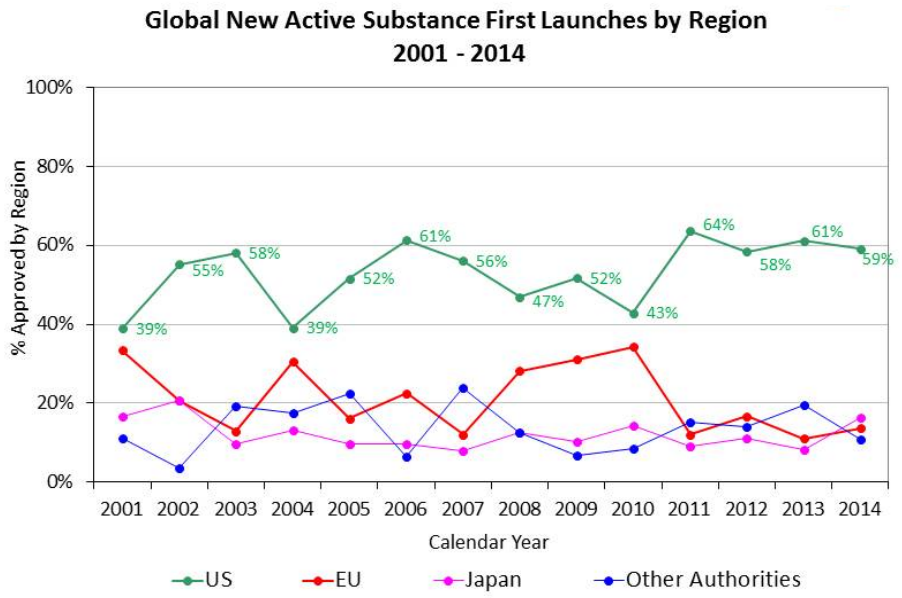


A Growing Record of Action on New Therapies

Each of the improvements noted above has contributed to speed both the development and the review of new therapies to prevent and fight disease. This past year provides an example of how those improvements are working; FDA approved 51 novel drugs and original biologics, 41 by CDER, 10 by CBER. Additionally, 21 of these 51 novel drugs were for orphan diseases.

The lag in approval times compared to approvals in other countries that existed many years ago has been reversed. Today, FDA approves drugs faster on average than all other developed nations: 40 days faster than Japan; 70 days faster than Canada; and 174 days faster than the European Union (EU). As the British-based Centre for Innovation in Regulatory Science recently reported, over 75 percent of the new drugs approved by Japan, EU, Canada, Australia, Switzerland, and FDA, from 2004 to 2013, were approved first by FDA. Yet, another independent analysis concludes that FDA

continues to lead the EU and other advanced regulatory authorities in the introduction of novel drugs, as shown by the graph below.



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

The most important effect of this progress is that American patients with untreatable or poorly treated diseases are receiving the newest therapies rapidly and well before their counterparts in other nations. In addition, the major enhancements that FDA has made in the drug safety surveillance system means that American patients can also be confident that these newly approved drugs continue to have intense scrutiny after they are marketed in the United States to detect any unexpected side effects and allow for quick and appropriate FDA action.

The Path Forward

Despite the progress that has been made, and as this Committee has noted, there are hurdles to overcome, if we are to ensure continued U.S. leadership in the biomedical sciences. While Congress and FDA have worked successfully together to greatly reduce FDA review times, many of the serious challenges for drug development occur before FDA review even begins. If the explosion in basic scientific knowledge is going

to efficiently translate into the treatments and cures patients need, we must work together to overcome critical infrastructure and scientific hurdles that prevent the advances we all desire. In January 2015, the Administration unveiled the Precision Medicine Initiative, a vital new research effort to catalyze improvements in targeting treatment to the right patient at the right time. Launched with a $215 million investment in the President's 2016 Budget, the Precision Medicine Initiative promises to arm clinicians with new tools, knowledge, and therapies that will work best for each patient. Below, I have described a few specific areas which advance the development of new therapies for patients.

Reducing Clinical Trial Costs

First, the cost of clinical trials continues to grow and is the greatest source of cost increases in medical product development. Today, developers of a new medicine spend many millions of dollars planning a clinical trial, developing an elaborate trial infrastructure, finding and enlisting investigators, conducting the trials, and managing the trial data. Each time a new drug is tested, the process is repeated, at great expense, only to dismantle the infrastructure when the study is completed.

We believe that there are ways to greatly improve clinical trial efficiency, such as widespread use of clinical trial networks and master protocols, and we would like to work with you to examine those possibilities.

Enhancing the Science of Biomarkers and Other Tools

Second, the science of identifying and evaluating the utility of biomarkers and other scientific tools must be greatly enhanced. These tools can be used to predict and evaluate the effects of candidate drugs, both before clinical testing, and in people. Biomarkers are technically defined as physical, biochemical, or genetic characteristics that are objectively measured and evaluated as indicators of health, disease, or in assessing the response to a therapeutic intervention. In other words, biomarkers are the results of tests done on the body, such as blood sugars or a chest x-ray. Biomarkers

have many uses in drug development, such as identifying appropriate patients to enroll in a clinical trial, performing safety monitoring, and selecting therapy for treating specific patients. Hundreds of biomarkers are used today in drug development. However, biomarkers based on new scientific understanding have been slow to come into clinical use, largely because the evidence supporting their validity has been lacking. The lack of new, well-understood biomarkers also impacts drug development, these new tests could speed evaluation of drug performance, including drug safety, and prediction of effectiveness. Similar to the problems with clinical trials, the scientific infrastructure for evaluating the validity of new biomarkers has not kept pace with the need for this activity.

Typically, drug sponsors interact with FDA about new biomarkers during clinical drug development, when an IND has been filed for a new molecule. These discussions are confidential, and while new biomarkers may be used in a specific drug development program, they are not necessarily subject to broad scientific scrutiny. To address this situation, CDER recently established a Biomarkers Qualification Program. In this program, biomarkers that have demonstrated performance for a certain use are designated by FDA as *qualified biomarkers*, and can be used during the regulatory process by any developer for that specific context of use. These qualified biomarkers are only a subset of the biomarkers FDA has used in the review process.

FDA recognizes that there is still confusion about how new biomarkers can be qualified through this process. Some believe that many biomarkers are “stalled” in the qualification process. The actual case is that most of the programs in the biomarker qualification process are still in the evidence-gathering stage–which may take considerable time due to the need for more development work within the scientific community.

However, it is important to note that biomarkers do not need to go through this formal qualification process, and most do not. As mentioned previously, FDA has the ability to work directly with drug sponsors who wish to utilize various new biomarkers within their

drug development program. For example, sponsors can propose a surrogate endpoint–one type of biomarker–to be used in clinical trials based upon the scientific communities' existing knowledge about the particular surrogate endpoint. A sponsor can request FDA's agreement on this surrogate endpoint through the "Special Protocol Assessment" process that is embodied in the PDUFA program. These product-specific surrogate endpoints are one example of biomarkers that do not need to pass through our formal qualification process in order to be used to support drug development and review. Biomarkers are also important in the growing field of so-called "personalized" or "precision" medicine, in which drugs are targeted at a genetically determined or other disease characteristic that only occurs in a subset of people with the disease. Targeted drug development is one of the most promising areas for future drug therapy. Patients are chosen for treatment based on specific test results (such as a genetic test or other biomarker), indicating that the patient's disease (tumor, hepatitis C, cystic fibrosis) is likely to respond to the drug.

About one-quarter of recent drug approvals are for targeted therapies.

In the early 1990s, targeted therapies represented only 5 percent of FDA's new drug approvals. In recent years, roughly one-quarter of the drug approvals has been supported by targeted drug development programs, and that rate appears to be growing over time. Important, new, recently approved, targeted cancer treatments include: Mekinst (trametinib) and Tafinlar (dabrafenib) for forms of melanoma; Imbruvica for forms of lymphoma and leukemia; and Zykadia (ceritnib) for a form of lung cancer. The development of such targeted therapies is clearly expanding rapidly. Similarly, targeted treatments for other diseases have been approved, including treatments for cystic fibrosis and ground-breaking treatments for hepatitis C that are potentially curative for the majority of treated patients. As targeted therapies become ubiquitous, advances in standardizing and increasing our understanding of the biomarkers that enable use of these therapies will be necessary.

Harnessing Evidence from Clinical Experience

Another source of information about drug effects is evidence from clinical experience (called "real world evidence" or "big data," by some). I have aggressively developed FDA's Sentinel Initiative, a national electronic system that is transforming FDA's ability to track the safety of drugs and biologics once they reach the market. Sentinel enables FDA to actively query diverse health care data sources–such as electronic health record systems, administrative and insurance claims databases, and registries–to evaluate possible medical product safety issues quickly and securely. The Sentinel Initiative is one of the largest uses of this type of information in health care and is proving vital for monitoring safety and analyzing safety signals. But the science of using evidence from clinical experience to establish product effectiveness, e.g., to evaluate new uses of drugs, is still in its infancy. So we must first develop the methodologies needed to harness its promise.

Strengthening Patient Engagement

The final example focuses on making patient experience more central to drug development. FDA recognizes that patients living with a chronic disease are experts in the effects of that disease and its current treatments. As you know, the FDA Safety and Innovation Act (FDASIA) instructed the Agency to begin a process for incorporating more patient experience into drug development, and we have had numerous public meetings to gain important insights from patients. But we recognize that information needs to be collected in a structured and representative way to be most useful in drug development. I hope that we can work with you to further the movement toward patient-focused drug development in your upcoming legislation.

CONCLUSION

There are other areas in which we hope to work with you as well, including modernizing drug manufacturing, encouraging the development of new antibiotics, and improving the processes for FDA review of drug/device combination products. I believe all of the

challenges I have described above are ones on which FDA, the drug industry, and patient groups have common interests. We look forward to working with Congress to address these challenges in ways that will serve patients and pharmaceutical innovation well.

Thank you again for inviting me to share my views today.

NOVEL DRUGS
APPROVED USING SURROGATE ENDPOINTS

In the last five years, FDA approved ***197 novel drugs and biologics; 84 relied upon surrogate endpoints.***

January 1, 2010 - December 31, 2014

Before the U.S. Food and Drug Administration (FDA) approves a drug or biologic, the product must show substantial evidence of effectiveness in clinical trials and that the benefits outweigh the risks. Clinical trials measure benefit using clinical endpoints, surrogate endpoints, or other types of measurements. Clinical endpoints measure how a patient feels or functions better, or lives longer. Surrogate endpoints are biomarkers, such as a laboratory test, radiographic image (e.g,. x-rays, MRIs), and physical sign (e.g., blood pressure), that substitute for clinical endpoints in certain circumstances.

A surrogate endpoint may serve as the basis for traditional approval when it is known, through scientific study, to predict clinical benefit. A surrogate endpoint may serve as a basis for Accelerated Approval when it is reasonably likely to predict a drug's intended clinical benefit. Drugs approved under Accelerated Approval are subject to the requirement of post-approval confirmatory trials.

From 2010-2014, FDA approved 197 novel drugs, known as new molecular entities (NMEs), and New Biologic Approvals that include both New Drug Applications (NDAs) and Biologic License Applications (BLAs). The following table shows the 84 NME drugs and original biologics approved during that time period that relied upon a surrogate endpoint for an approval determination (i.e., traditional approval or Accelerated Approval). Many of these drugs have orphan designation, which means that they are intended to treat rare or uncommon diseases.

Approval Date	Drug Name	Abbreviated Indication*	Traditional Approval	Accelerated Approval**	Orphan Designation	Surrogate Endpoint
1/25/2010	Victoza (liraglutide)	Type 2 Diabetes Mellitus	✓			Hemoglobin A1C (HgA1C)
2/19/2010	Menveo	prevention of meningococcal A, C, Y, and W-135 infection	✓			Immunogenicity
2/24/2010	Prevnar13	prevention of invasive pneumococcal infection	✓			Immunogenicity
2/26/2010	Vpriv (velaglucerase alfa)	Type 1 Gaucher Disease	✓		✓	Hemoglobin (Hgb)
3/18/2010	Carbaglu (carglumic acid)	urea cycle disorder, N-acetylglutamate synthetase (NAGS) deficiency	✓		✓	Ammonia, glutamine, citrulline levels
5/24/2010	Lumizyme (alglucosidase alfa)	non-infantile onset Pompe disease (8 years and older)	✓		✓	Forced Vital Capacity (FVC) ***
6/1/2010	Prolia (denosumab)	osteoporosis	✓			vertebral fractures on xray
7/10/2010	Alpha-1-Proteinase Inhibitor (Human)	treatment of alpha-1-proteinase inhibitor deficiency	✓		✓	Protein levels
9/14/2010	Krystexxa (pegloticase)	gout	✓		✓	plasma uric acid level
11/10/2010	Egrifta (tesamorelin for injection)	Lipodystrophy in human immunodeficiency virus (HIV) patients	✓			percent change in visceral fat by computerized tomography (CT) scan
2/17/2011	Factor XIII Concentrate (Human)	prophylactic treatment of factor XIII deficiency		✓	✓	Pharmacokinetics
2/25/2011	Edarbi (azilsartan medoxomil)	hypertension	✓			Blood pressure (BP)
2/28/2011	Daliresp (roflumilast)	chronic obstructive pulmonary disease (COPD)	✓			Forced expiratory volume in 1 second (FEV1) ***
3/16/2011	Adenovirus Vaccine, Live, Oral Type 4 and Type 7	prevention of infection with two adenovirus types	✓			Immunogenicity (for Type 7)
4/6/2011	Caprelsa (vandetanib)	Medullary thyroid cancer	✓		✓	Progression Free Survival (PFS)
5/2/2011	Tradjenta (linagliptin)	Type 2 Diabetes Mellitus	✓			Hemoglobin A1C (HgA1C)
5/13/2011	Victrelis (boceprevir)	hepatitis C genotype 1	✓			Sustained Viral Response (SVR)

Approval Date	Drug Name	Abbreviated Indication*	Traditional Approval	Accelerated Approval**	Orphan Designation	Surrogate Endpoint
5/20/2011	Edurant (rilpivirine)	human immunodeficiency virus (HIV)	✓			viral load
5/23/2011	Incivek (telaprevir)	hepatitis C genotype 1	✓			Sustained Viral Response (SVR)
6/15/2011	Nulojix (belatacept)	organ rejection prophylaxis	✓		✓	biopsy-proven acute rejection (BPAR)
7/1/2011	Arcapta Neohaler (indacaterol maleate)	chronic obstructive pulmonary disease (COPD)	✓			Forced expiratory volume in 1 second (FEV1)
8/19/2011	Adcetris (brentuximab vedotin)	1) Hodgkin's Lymphoma; 2) Systemic anaplastic large cell lymphoma		✓	✓	1) Overall objective response rate (ORR) using computerized tomography (CT) or positron emission tomography (PET) scans; 2) overall response rate (ORR)
8/26/2011	Xalkori (crizotinib)	non-small cell lung cancer (NSCLC), anaplastic lymphoma kinase (ALK) positive mutation		✓	✓	Objective response rate (ORR) using computerized tomography (CT) or magnetic resonance imaging (MRI)
10/14/2011	Ferriprox (Deferiprone)	Transfusional iron overload due to thalassemia		✓	✓	serum ferritin
11/16/2011	Jakafi (ruxolitinib)	myelofibrosis	✓		✓	Percent reduction in spleen volume by computerized tomography (CT) or magnetic resonance imaging (MRI)
11/18/2011	Erwinaze (asparaginase erwinia chrysanthemi)	acute lymphoblastic leukemia (ALL)	✓		✓	trough asparaginase activity level
1/17/2012	Voraxaze (glucarpidase)	methotrexate (MTX) toxicity	✓		✓	plasma methotrexate (MTX) levels
1/27/2012	Inlyta (axitinib)	renal cell carcinoma (RCC)	✓			Progression Free Survival (PFS)
1/30/2012	Erivedge (vismodegib)	basal cell carcinoma	✓			Objective response rate (ORR)
1/31/2012	Kalydeco (ivacaftor)	cystic fibrosis, G551D mutation	✓		✓	Forced expiratory volume in 1 second (FEV1)
2/10/2012	Zioptan (tafluprost)	glaucoma	✓			intraocular pressure (IOP)
3/27/2012	Omontys (peginesatide)	anemia in chronic kidney disease	✓			Hemoglobin (Hgb)
5/1/2012	Elelyso (taliglucerase alfa)	Type 1 Gaucher Disease	✓		✓	spleen volume by magnetic resonance imaging (MRI)

Approval Date	Drug Name	Abbreviated Indication*	Traditional Approval	Accelerated Approval**	Orphan Designation	Surrogate Endpoint
6/8/2012	Perjeta (pertuzumab)	HER-2 positive metastatic breast cancer	✓			Progression Free Survival (PFS)
6/14/2012	MenHibrix	prevention of meningococcal A and C and haemophilus influenzae B infection	✓			Immunogenicity
7/20/2012	Kyprolis (Carfilzomib)	multiple myeloma		✓	✓	Overall response rate (ORR) by International Myeloma Working Group (IMWG) criteria
7/23/2012	Tudorza Pressair (aclidinium bromide)	chronic obstructive pulmonary disease (COPD)	✓			Forced expiratory volume in 1 second (FEV1)
8/27/2012	Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate)	human immunodeficiency virus (HIV)	✓			viral load
8/29/2012	tbo-filgrastim	chemotherapy-induced neutropenia	✓			absolute neutrophil count (ANC)
9/4/2012	Bosulif (bosutinib)	chronic myelogenous leukemia (CML)	✓		✓	Major Cytogenetic Response (MCyR)
10/17/2012	Jetrea (ocriplasmin)	vitreomacular adhesion (VMA)	✓			Vitreomacular adhesion (VMA) by central reading
10/26/2012	Synribo (omacetaxine mepesuccinate)	chronic myelogenous leukemia (CML)		✓	✓	Major Hematologic Response (MaHR)
11/29/2012	Cometriq (Cabozantinib)	Medullary thyroid cancer	✓		✓	Progression Free Survival (PFS)
12/14/2012	Iclusig (ponatinib)	chronic myeloid leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL)		✓	✓	Major Cytogenetic Response (MCyR) and Major Hematologic Response (MaHR)
12/14/2012	Signifor (pasireotide diaspartate)	Cushing's disease	✓		✓	urine free cortisol level
12/21/2012	Juxtapid (lomitapide)	homozygous familial hypercholesterolemia (HoFH)	✓		✓	Serum low-density lipoprotein-cholesterol (LDL-C)
12/28/2012	Sirturo (bedaquiline)	Multidrug resistant (MDR) pulmonary tuberculosis (TB)		✓	✓	time to sputum culture conversion

Approval Date	Drug Name	Abbreviated Indication*	Traditional Approval	Accelerated Approval**	Orphan Designation	Surrogate Endpoint
1/25/2013	1) Nesina (alogliptin); 2) Osena (alogliptin/ pioglitazone); 3) Kazano (alogliptin/metformin)	Type 2 Diabetes Mellitus	✓			Hemoglobin A1C (HgA1C)
1/29/2013	Kynamro (mipomersen)	homozygous familial hypercholesterolemia (HoFH)	✓		✓	serum low-density lipoprotein-cholesterol (LDL-C)
2/8/2013	Pomalyst (pomalidomide)	multiple myeloma		✓	✓	Overall response rate (ORR) by European Group for Blood and Bone Marrow Transplant (EGBMT) criteria
2/22/2013	Kadcyla (ado-trastuzumab emtansine)	HER-2 positive metastatic breast cancer	✓			Progression Free Survival (PFS) using computerized tomography (CT) or magnetic resonance imaging (MRI) ***
2/26/2013	Osphena (ospemifene)	dyspareunia and/or vaginal dryness due to vulvar and vaginal atrophy	✓			parabasal and superficial cell maturation index on vaginal smear and vaginal pH***
3/29/2013	Invokana (canagliflozin)	Type 2 Diabetes Mellitus	✓			Hemoglobin A1C (HgA1C)
5/10/2013	Breo Ellipta (fluticasone furoate and vilanterol trifenatate)	chronic obstructive pulmonary disease (COPD)	✓			Forced expiratory volume in 1 second (FEV1)
5/29/2013	Mekinist (trametinib)	unresectable or metastatic melanoma with BRAF V600E or V600K mutations	✓		✓	Progression Free Survival (PFS)
5/29/2013	Tafinlar (dabrafenib)	unresectable or metastatic melanoma with BRAF V600E or V600K mutations	✓		✓	Progression Free Survival (PFS)
7/12/2013	Gilotrif (afatinib)	NSCLC with epidermal growth factor receptor (EGFR) exon 19 deletaions or exon 21 (L858R) substitution mutations	✓		✓	Progression Free Survival (PFS)
8/12/2013	Tivicay (dolutegravir)	human immunodeficiency virus (HIV)	✓			viral load

Approval Date	Drug Name	Abbreviated Indication*	Traditional Approval	Accelerated Approval**	Orphan Designation	Surrogate Endpoint
10/3/2013	Duavee (conjugated estrogens/bazedoxifene)	osteoporosis	✓			Bone marrow density (BMD) at lumbar (L)-spine
11/1/2013	Gazyva (obinutuzumab)	chronic lymphocytic leukemia (CLL)	✓		✓	Progression Free Survival (PFS)
11/13/2013	Imbruvica (ibrutinib)	mantle cell lymphoma (MCL)		✓	✓	Overall response rate (ORR)
11/22/2013	Olysio (simeprevir)	hepatitis C genotype 1	✓			Sustained Viral Response (SVR)
12/6/2013	Sovaldi (sofosbuvir)	hepatitis C genotypes 1, 2, 3 or 4	✓			Sustained Viral Response (SVR)
12/18/2013	Anoro Ellipta (umeclidinium and vilanterol)	chronic obstructive pulmonary disease (COPD)	✓			Forced expiratory volume in 1 second (FEV1)
1/8/2014	Farxiga (dapagliflozin)	Type 2 Diabetes Mellitus	✓			Hemoglobin A1C (HgA1C)
2/24/2014	Myalept (metreleptin)	leptin deficiency	✓		✓	Hemoglobin A1C (HgA1C)
4/15/2014	Tanzeum (albiglutide)	Type 2 Diabetes Mellitus	✓			Hemoglobin A1C (HgA1C)
4/23/2014	Sylvant (siltuximab)	multi-centric Castleman's disease (MCD) who are HIV and human herpes virus-8 (HHV-8) negative	✓		✓	Overall response rate (ORR)***
4/29/2014	Zykadia (ceritinib)	anaplastic lymphoma kinase (ALK) positive non-small cell lung cancer (NSCLC)		✓	✓	Overall response rate (ORR)
7/3/2014	Beleodaq (belinostat)	peripheral T-cell lymphoma (PTCL)		✓	✓	Overall response rate (ORR)
7/23/2014	Zydelig (idelalisib)	1) Chronic lymphocytic leukemia (CLL); 2) Follicular B-cell non-Hodgkin lymphoma (FL) and small lymphocytic lymphoma (SLL)	✓[1]	✓[2]	✓	1) Progression Free Survival (PFS); 2) overall response rate (ORR)
7/31/2014	Striverdi Respimat (olodaterol)	Chronic obstructive pulmonary disease (COPD)	✓			Forced expiratory volume in 1 second (FEV1)

[1] for CLL indication
[2] for FL and SLL indications

Approval Date	Drug Name	Abbreviated Indication*	Traditional Approval	Accelerated Approval**	Orphan Designation	Surrogate Endpoint
8/1/2014	Jardiance (empagliflozin)	Type 2 Diabetes Mellitus	✓			Hemoglobin A1C (HgA1C)
8/19/2014	Cerdelga (eliglustat)	Type 1 Gaucher Disease	✓		✓	spleen volume
9/4/2014	Keytruda (pembrolizumab)	unresectable or metastatic melanoma		✓	✓	tumor response rate by computerized tomography (CT) and magnetic resonance imaging (MRI)
9/18/2014	Trulicity (dulaglutide)	Type 2 Diabetes Mellitus	✓			Hemoglobin A1C (HgA1C)
10/10/2014	Harvoni (ledipasvir and sofosbuvir)	hepatitis C genotype 1	✓			Sustained Viral Response (SVR)
10/15/2014	Esbriet (pirfenidone)	idiopathic pulmonary fibrosis (IPF)	✓		✓	Forced Vital Capacity (FVC)
10/15/2014	Ofev (nintadanib)	idiopathic pulmonary fibrosis (IPF)	✓		✓	Forced Vital Capacity (FVC)
10/29/2014	Trumenba	prevention of meningococcal B infection		✓		Immunogenicity
12/3/2014	Blincyto (blinatumomab)	B-cell precursor acute lymphoblastic leukemia (ALL)		✓	✓	Complete remission (CR) or complete remission with partial hematological recovery (CRh)
12/19/2014	Viekira Pak (ombitasvir / paritaprevir / ritonavir / dasabuvir)	hepatitis C genotype 1	✓			Sustained Viral Response (SVR)
12/19/2014	Lynparza (olaparib)	advanced ovarian cancer with deleterious or suspected deleterious germline BRCA mutations		✓	✓	Objective response rate (ORR)
12/22/2014	Opdivo (nivolumab)	unresectable or metastatic melanoma		✓	✓	Objective response rate (ORR)

* Please see full indication in product labeling.

** There were 36 total Accelerated Approvals (AAs) for 2010-2014 including new and supplemental NDAs and BLAs as well as AAs based on intermediate clinical endpoints. 18 of those 36 AAs were for novel NME drugs and original biologics approved using surrogate endpoints—these are listed in the table.

*** Approval determination relied upon a surrogate endpoint and a direct clinical benefit; only the surrogate endpoint is listed in the table.

Please note: The information provided in the table is preliminary and should be considered a work-in-progress, as there is no established definition for “surrogate endpoint” vs. “clinical outcome assessment”.