DEPARTMENT OF HEALTH AND HUMAN SERVICES

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# STATEMENT OF

JESSE L. GOODMAN, M.D., M.P.H.

CHIEF SCIENTIST AND

DEPUTY COMMISSIONER FOR SCIENCE AND PUBLIC HEALTH

FOOD AND DRUG ADMINISTRATION

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INTRODUCTION

Good afternoon, Chairman Harkin and Members of the Committee. I am Dr. Jesse L. Goodman, Chief Scientist and Deputy Commissioner for Science and Public Health at the Food and Drug Administration (FDA), an agency of the Department of Health and Human Services. I appreciate the opportunity to be here today to describe the role of FDA in encouraging and speeding the development of drugs, vaccines, devices, and diagnostic tests to improve the lives of children affected by rare diseases.

There are more than 7,000 rare diseases, defined by the Orphan Drug Act (ODA) as diseases affecting fewer than 200,000 people in the U.S., and many of these affect children. Some diseases, such as severe genetic diseases, predominantly or exclusively affect children. As a practicing physician and a researcher specializing in infectious diseases and trained in oncology, I have personally witnessed the devastating human face of diseases like these.

While we have made great progress in addressing this challenge, there are still an estimated 20 million Americans suffering from rare diseases for which there are no approved therapies available. Factors responsible for this are only magnified for children. In many cases, and even when the basic scientific problem is understood, the applied scientific knowledge is still not there to identify or develop good candidates. In addition, market incentives may be insufficient to drive the sustained commercial interest and investment necessary to develop new medical products for pediatric rare diseases. Furthermore, conducting clinical trials to treat this population presents real challenges. As with all rare diseases, the number of patients available for clinical trials is small, and our knowledge about the history and best management of these diseases is often limited. Small populations are made even smaller when we consider that

diseases and therapies may affect children differently at different ages—and not all children are the same. A product that is effective in an infant may not work for an older child or a teen. In addition, with limited information about rare diseases, we may have difficulty determining whether a child's response to therapy in a clinical study is related to intervention with a medical product or is a result of the natural course of the disease over his or her lifetime. Other factors that impact all clinical trials in children, such as limitations on the amount of blood that can be drawn from a child, also come into play. All of these issues complicate progress in this area.

In the face of these challenges, FDA believes it can contribute collaboratively to achieve progress, and we are taking a multifaceted approach to supporting the development of medical products for pediatric rare diseases. I welcome your shared interest and commitment to this issue, and I am pleased to be here today to provide you with an overview of our major efforts to enhance the development and availability of products that can improve the lives of those affected by pediatric rare diseases.

Congress has empowered FDA with many innovative tools to help address pediatric rare diseases. I will begin by providing a summary of the statutory authorities under which we are currently conducting these efforts, followed by a discussion of other related activities at FDA.

## FDA STATUTORY AUTHORITIES TO ADDRESS PEDIATRIC RARE DISEASES

### The Orphan Drug Act

The 1983 Orphan Drug Act (ODA) created financial incentives, including grants, to support the development of new drugs for people with rare diseases. Under this system, developers of promising drugs or biologics can, prior to submitting applications for approval of those products, apply to receive "orphan drug status" designation. If products so designated are subsequently

shown to be safe and effective and receive marketing approval, their developers receive market exclusivity for seven years.

FDA's Office of Orphan Products Development (OOPD) serves as a focal point for FDA's efforts to address rare diseases, and can provide significant assistance to scientists who may lack product development and regulatory experience. OOPD also fosters new approaches throughout FDA to advance development of therapies for rare diseases. For example, last month OOPD announced the availability of a new tool, the Rare Disease Repurposing Database, which identifies drugs that are deemed promising for rare illnesses and are already approved by FDA for another disease. A novel feature and major advantage of this database is that it focuses on drugs that have already gone through the FDA approval process. Thus, repurposing of these drugs for a new rare disease indication might be attainable quickly, relatively inexpensively, and at great benefit to the patients involved.

ODA has been extremely successful in changing the landscape and success rate of orphan drugs and improving the lives of many patients. Prior to the existence of ODA, there were few new products for people with rare diseases, but, since 1983, more than 2,150 medical therapies have been officially designated as "orphans," and 358 of these therapies have gone on to full marketing approval. Of these products, approximately 67 (19 percent) are for diseases that occur exclusively among children and 201 (57 percent) of these are for diseases that occur among both children and adults. ODA also established FDA's largest grants program, $15.2 million for FY 2010, managed by OOPD. Forty-seven products have been found to be safe and effective as a result of data generated in part by those grant monies. Of these products, approximately 11 (24 percent) are for diseases that occur exclusively among children and 28 (62 percent) of these are for diseases that occur among both children and adults.

The approved products now on the market that qualified for orphan product designation are a testament to the important accomplishments and successes of the program. Success stories include:

- Carbaglu (carglumic acid) for the treatment of NAGS deficiency, the rarest of the Urea Cycle Disorders, which are diseases that lead to elevated ammonia levels in the blood and cause seizures, poor muscle tone, respiratory distress, coma, and even death. NAGS deficiency affects fewer than 10 patients in the United States at any given time. This drug was approved in March 2010, based on a case series in 23 patients.
- Myozyme (alglucosidase alfa) for the treatment of Pompe Disease, which is a rare genetic disease resulting in progressive skeletal and respiratory muscle weakness caused by an accumulation of glycogen (a carbohydrate). About 1,000-2,000 patients in the United States suffer from Pompe Disease, of which only a few hundred are infants. In infants, the disease can be rapidly fatal due to respiratory failure. This drug was approved in April 2006, based on the results of a single, pivotal study in 18 patients.
- Ceprotin (Protein C Concentrate) for treatment of severe congenital Protein C deficiency, the prevention and treatment of venous thrombosis (blood clots in the vein), and purpura fulminans (life-threatening bleeding and tissue death). The life-threatening form of the disease affects about 1 in 500,000 to 1 in 750,000 newborns. This drug was approved in March 2007, based on a clinical study involving 18 patients.
- Kogenate FS (Antihemophilic Factor (Recombinant)) to prevent bleeding episodes and the risk of joint damage in children with hemophilia A. The disease affects about 15,000 individuals in the United States, nearly all of whom are male. This drug was approved for this indication in October 2008, based on a clinical development program of 65 boys under 30 months of age.

**Best Pharmaceuticals for Children Act and Pediatric Research Equity Act**

Under the leadership of Senator Dodd and the Members of this Committee, over the past decade, Congress created and reauthorized two critical programs that have dramatically improved the practice of medicine for children: the Best Pharmaceuticals for Children Act (BPCA), first enacted in 1997 as part of the Food and Drug Administration Modernization Act, and the Pediatric Research Equity Act (PREA), first enacted in 2003. Together, BPCA and PREA create a "carrot and stick" approach to the development of important new safety, effectiveness, and dosing information for medical products used in children. BPCA is an incentive program that grants market exclusivity to sponsors that elect to study their product in children according to protocols set by FDA. PREA gives FDA the authority to require pediatric studies under certain conditions. Before these laws were enacted, an estimated 80 percent of medication labels did not include information about use in children. Without pediatric studies, doctors treating children most often have to use medical products without important information about correct dosage or safety and effectiveness. Today, using the tools that Congress provided with BPCA and PREA, we have worked with industry to add new pediatric information to the labels of 385 products.

The Food and Drug Administration Amendments Act of 2007 (FDAAA) established the Office of Pediatric Therapeutics (OPT) within FDA's Office of the Commissioner. Its primary mission is to ensure access for children to innovative, safe, and effective medical products. OPT includes four distinct yet interrelated programs to support FDA efforts to improve pediatric access to medical products:

- The OPT Ethics Program supports FDA efforts to ensure that children are only enrolled in clinical studies which are both scientifically necessary and ethically appropriate.

- The OPT Safety Program coordinates the mandated review by the Pediatric Advisory Committee of the safety of drug and biologic products one year after labeling changes, in response to voluntary and required pediatric studies.
- The OPT Scientific Activities Program works with FDA scientists and reviewers to ensure that pediatric studies are rigorously designed and conducted in accord with current scientific understanding of such issues as exposure-response and extrapolation.
- The OPT International Program facilitates communication and collaboration between FDA and partner regulatory agencies around the world as well as other regions, such as Europe.

**The Priority Review Voucher Program**

FDA has long had in place a review system to ensure that the most critical medical products are reviewed on a priority basis. Priority review applications for products that treat life-threatening and serious diseases are reviewed in a six-month period, compared to the ten-month period for other products. Most products to treat pediatric rare diseases are entitled to get this quicker review cycle, which does assist in getting needed products to market more quickly

Thanks to the leadership of Senator Brown and others, the FDAAA granted FDA the authority, beginning in 2009, to award priority review vouchers to a company that submits and, after review, receives marketing approval for a product for one of 16 neglected "tropical" diseases listed in the legislation. While these diseases are not rare in the global context, they often affect fewer than 200,000 individuals in the United States and are therefore eligible for orphan drug status designation. If transferred to apply to a blockbuster drug, the four months of earlier market access available when a priority review voucher is redeemed could translate into an incentive worth hundreds of millions of dollars. Already, one such voucher has been issued to

Novartis, for its anti-malarial drug Coartem (artemether, lumefantrine). FDA has informed major human pharmaceutical companies that also own veterinary medicines that appear promising for neglected human diseases that they could qualify for a priority review voucher if evaluation for human disease indications supported marketing approval for one of 16 neglected diseases listed in the legislation.

**The Humanitarian Device Exemption Program**

Also included in FDAAA is the Pediatric Medical Device Safety and Improvement Act, which expanded the Humanitarian Device Exemption (HDE) program. The HDE program provides an exemption from the otherwise applicable effectiveness requirements for devices that are designed to treat or diagnose diseases or conditions that affect fewer than 4,000 individuals in the United States per year. To qualify for this exemption, certain criteria must be met, including a determination by FDA that the probable benefit outweighs the risk of injury or illness from use of the device. FDAAA provided an additional incentive for development of devices intended for treatment or diagnosis of rare pediatric diseases by lifting certain restrictions on charging for the device. An example of a device granted an HDE is the adjustable titanium rib for children with thoracic insufficiency syndrome, a condition where the child's chest cannot support normal growth of the lungs or spine. This device prevents the child's body from collapsing on itself, allowing for growth and maturation of lungs and spine in patients who otherwise might not survive. The inventor, an orthopedic surgeon, recognized the need for a device that could be adjusted as a child grows.

FDAAA also established a grants program to fund pediatric device consortia that facilitate the development, production, and distribution of medical devices for children. These consortia serve to connect pediatric medical device innovators with potential manufacturers and provide advice

and assistance. So far, four consortia have been established. Since their inception in October of 2009, the consortia have assisted in the evaluation and development of more than 50 pediatric medical devices, including development of a critical pediatric ventricular assist device, which (at least on a temporary basis) partially or completely replaces heart function for children with heart disease while they await a transplant.

## ADDITIONAL FDA EFFORTS TO ADDRESS PEDIATRIC RARE DISEASES

### Establishment of Rare Diseases Director Position Within FDA Center

Expanding on its commitment to facilitate the development and approval of safe and effective drugs for Americans with rare diseases, in February 2010, FDA created a position of Associate Director for Rare Diseases in the Center for Drug Evaluation and Research (CDER). In conjunction with OOPD, the Associate Director for Rare Diseases supports collaboration among scientists and clinicians throughout FDA, including with the Office of Pediatric Therapeutics, promoting scientific and regulatory innovations to help facilitate timely development and approval of new treatments for patients with rare diseases.

### Training and Collaboration to Support Rare Disease Product Development

Since 2008, FDA has sponsored an annual course designed to teach FDA reviewers and other interested clinicians the science of conducting and analyzing small clinical trials, which are especially useful for testing medical products for pediatric rare diseases. In October 2010, FDA will co-sponsor a larger and more comprehensive Annual Rare Disease Investigator Training Course, in collaboration with the National Institutes of Health (NIH) and the National Organization for Rare Disorders (NORD). FDA is planning a series of scientific workshops to address important and difficult rare disease research issues, and is developing a "rare disease database" to establish the natural history of rare diseases to assist with planning trials to test rare

disease therapies. Lastly, FDA is enhancing collaborations to increase transparency, share advice, and establish new programs with several pertinent organizations, including NORD; NIH's Office of Rare Diseases Research, Therapeutics for Rare and Neglected Diseases Program, and other NIH Institutes and Centers; patient advocacy groups; academia; and the Institute of Medicine (IOM).

**FDA Rare and Neglected Disease Review Groups**

Section 740 of the FY 2010 Appropriation Act (Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriation Act, 2010, Public Law 111-80) directed FDA to establish internal review groups to address rare and neglected diseases, to report to Congress one year after establishing the review groups and to issue guidance relating to rare and neglected diseases. To implement section 740, in March 2010, FDA established two new expert working groups, the Rare Disease Review Group and the Neglected Disease Review Group. Last month, a meeting was held on rare diseases, at which 26 speakers provided comments. Those comments will be made available when FDA finalizes its report to Congress on March 11, 2011. A similar meeting to discuss neglected diseases is planned for September. Finally, FDA and NIH are co-sponsoring an IOM study, which began in the fall of 2009, to review national policy for rare disease research and related medical product regulation. The results and recommendations of that study are due at the end of September 2010, and FDA review groups will consider the IOM study findings in their ongoing work.

**Office of Special Health Issues**

FDA's Office of Special Health Issues (OSHI) serves as a liaison between FDA and patients, patient advocates, health professionals, and their representative organizations. OSHI staff

encourages and supports active participation of these stakeholders in forming FDA regulatory policy to ensure the Agency's decisions are based upon a full range of perspectives. OSHI also is responsible for communicating important safety and regulatory information to health professionals and patients. This office is a resource to patients with rare diseases who have questions about FDA-regulated products or seek access to investigational new products. It is also a resource for parents whose children are suffering from rare diseases.

**The Role of Regulatory Science**

Researchers have now defined the genetic basis of more than 2,000 rare diseases and identified potential drug targets for many rare and neglected diseases. However, a large gap exists between advances in basic scientific research and needed applied product development and evaluation research, a gap that contributes to the lack of real products getting to patients for many such diseases, despite advances in basic sciences. This gap can be filled in part through enhanced regulatory science, which is the development of tools, methods, assays, standards, and models that help speed and improve the development, review, and approval of innovative products.

The President's FY 2011 budget for FDA includes dedicated funding for the Agency to strengthen its critical scientific capacity to leverage the opportunities provided by 21st-century science and to enhance its scientific collaborations. In February 2010, FDA and NIH announced a new collaboration on regulatory and translational science to help speed the translation of research into medical products and therapies, and we see real opportunities in working together to help move promising therapies for rare and neglected diseases from concepts to realities.

Through collaboration, FDA will foster new opportunities for patients and consumers. Regulatory science at FDA holds great promise for bridging the gap in our scientific knowledge

about how medical treatments impact children specifically and for unlocking their potential for children. For example, during the 2009 influenza pandemic, FDA's regulatory science work on dosing of the antiviral drug Tamiflu (oseltamivir phosphate) in children under the age of one year was adopted by countries around the world. As another example, FDA scientists from the Agency's Center for Biologics Evaluation and Research originated a collaborative effort with the National Toxicology Program to improve the safety of gene therapies, in order to design vectors that can deliver needed curative genes to children with genetic diseases, but without the serious risk of malignancy seen in some studies.

Enhanced regulatory science at FDA also is intended to inform and strengthen our review processes and interactions. Strong science, whether lab-based, clinical, or involving population and statistical sciences, is critical in supporting the kind of intensely interactive review processes that we know can improve the odds of success in product development. This is particularly true for diseases where experience is limited or to support product developers with more limited experience. FDA scientists can meet with sponsors early in product development, even before human studies are planned, to help identify and resolve critical issues and provide input on proposed development plans. Such meetings, and continued high quality scientific interactions, while labor intensive, are particularly critical in identifying and resolving scientific issues with respect to products for pediatric rare diseases.

## CONCLUSION

FDA's multifaceted and collaborative approach to addressing the obstacles of product development for pediatric rare diseases has resulted in many successes and real progress, but

much more work remains to be done to meet the tremendous needs of this population. Through the statutes already in place, Congress has granted FDA important authorities that we have found very useful to help address this challenge. In addition, both new initiatives and enhanced efforts engaging many FDA components, including in interactive review and regulatory support for sponsors, collaboration and training, and in regulatory science, are underway to facilitate development and evaluation of needed products. We look forward to continuing to work with you and our colleagues in the public health arena to address the challenges that we face. Thank you again for this opportunity to discuss pediatric rare diseases. I welcome your comments and questions.