

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

FDA's Efforts on Rare and Neglected Diseases

Witness appearing before the  
Senate Appropriations Subcommittee on  
Agriculture, Rural Development, Food and Drug Administration,  
and Related Agencies

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June 23, 2010

## **INTRODUCTION**

Good afternoon Chairman Kohl and Members of the Subcommittee. I am Dr. Jesse L. Goodman, Chief Scientist and Deputy Commissioner for Science and Public Health at the Food and Drug Administration (FDA). I appreciate the opportunity to be here today to describe the role of FDA in encouraging and speeding the development of drugs, vaccines, and diagnostic tests for rare and neglected diseases.

There are more than 6,000 rare diseases, defined by the Orphan Drug Act as a disease affecting fewer than 200,000 people in the U.S., and numerous neglected diseases that predominantly affect impoverished or disenfranchised populations of the developing world. Around the world, more than one billion people are affected by at least one neglected disease, such as tuberculosis (TB), malaria, hookworm infection, and leprosy. As a practicing physician and a researcher specializing in infectious diseases and also trained in oncology, I have personally witnessed the devastating human face and social impacts of many of these diseases.

As a physician and a public health official, I want to take this opportunity to remind our nation that infectious diseases know no boundaries. Threats to health anywhere are threats to everyone. Witness the risks to the U.S. from multi-drug resistant TB and the disruption that a single infected traveler caused in 2007. In May 2010, the Centers for Disease Control and Prevention (CDC) reported that, for the first time, cases of dengue — the most common mosquito-borne viral disease, causing 50 to 100 million infections and 25,000 deaths each year around the world — were identified in Florida residents who had not traveled overseas. Thus, there are compelling global humanitarian as well as U.S. health and national security reasons to bring the best possible science to bear in protecting against what are often considered “tropical diseases.”

Yet, for both rare diseases and diseases that are perceived to affect primarily poor regions and people, market incentives are often lacking to drive the commercial interest and investment critical for developing medical products. In addition, some of the major diseases, such as malaria, TB and HIV, present scientifically formidable challenges in drug and vaccine development. Finally, clinical studies of rare diseases, or of diseases occurring in resource poor environments, are often hard to accomplish. For all of these reasons, the needs and opportunities are enormous and FDA can help make a real difference.

I welcome your shared interest and commitment to this issue and 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 rare and neglected diseases.

## **THE ORPHAN DRUG ACT AND FDA**

The 1983 Orphan Drug Act (ODA) created financial incentives, including grants, for the developers 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 for their products. 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 Office of Orphan Products Development (OOPD) serves as the contact for all parties interested in making new therapies for people with rare diseases, often providing 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 week 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 357 of these therapies have gone on to full marketing approval. This program also benefits those affected by rare and neglected diseases, as drugs for the treatment of the neglected diseases of the developing world generally also qualify as orphan drugs because most neglected diseases affect fewer than 200,000 persons in the United States.

OOPD’s engagement in the area of neglected diseases is exemplified by an ongoing project to stimulate manufacturers to identify and evaluate for potential human use certain products approved for the treatment of intestinal parasites in veterinary medicine.

The FDA Amendments Act of 2007 (FDAAA) granted FDA the authority to award priority review vouchers beginning in 2009 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. Under the law, developers of treatments for neglected diseases are rewarded with

priority review vouchers to be applied to other drugs, such as profitable cardiovascular therapies, that would not otherwise qualify for such an expedited review. For a blockbuster drug, these four months of earlier market access could translate into hundreds of millions of dollars.

Already, one such voucher has been issued to Novartis, for its anti-malarial drug Coartem.

OOPD 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.

ODA has established FDA's largest grants program, \$15.2 M 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. The humanitarian use device (HUD) program is another legislative program established in 1990, which creates an alternative pathway for getting market approval for medical devices that help people with rare diseases. For example, the adjustable titanium rib, which for children with thoracic insufficiency syndrome prevents the child's body from collapsing on itself, was a HUD-designated device invented by a pediatric orthopedic surgeon who received an OOPD grant; this surgeon recognized the need for such a device that could be adjusted as a child grows. Also, in 2007 Congress established a system of pediatric device consortia, also administered by OOPD, for creating new medical devices for children.

Along with a rapid expansion in new drugs for people with rare diseases, the 27 years since enactment of ODA have seen remarkable growth in the biotech industry. The incentives offered by ODA motivated investments by biotech firms in products aimed at rare diseases, and the

financial success of key biotech companies has further stimulated this sector. Consequently, ODA's fundamental principles have been adopted by many other countries, most notably by the European Medicine's Agency (EMA) in 1999. While FDA remains the world leader in orphan drug regulation, this international expansion of ODA, combined with internet linkages among patient groups and a pharmaceutical industry without borders, has made global harmonization an important component of the work at OOPD. Accordingly, EMA and FDA now have a joint application form for orphan designation.

## **FDA EFFORTS TO ENHANCE DEVELOPMENT AND REVIEW OF PRODUCTS TO TREAT RARE DISEASES**

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). The activities led by the Associate Director for Rare Diseases complement the work of FDA's OOPD.

The Associate Director for Rare Diseases serves as CDER's focal point within the Center and to the rare disease drug development community and assists stakeholders and developers of drug and biologic products in navigating the complex regulatory requirements for bringing safe and effective treatments to patients in need. In conjunction with OOPD, the Associate Director for Rare Diseases supports collaboration among scientists and clinicians throughout FDA, promoting scientific and regulatory innovations to help facilitate timely development and approval of new treatments for patients with rare diseases.

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 rare diseases. In October 2010, FDA will co-sponsor the 1<sup>st</sup> Annual Rare Disease Investigator Training Course, in collaboration with 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 Office of Rare Diseases Research (ORDR), Therapeutics for Rare and Neglected Diseases Program (TRND), the National Institute of Neurological Disorders and Stroke (NINDS), patient advocacy groups, academia, and the Institute of Medicine.

FDA is fully committed to applying the requisite flexibility in the development and review of products for rare diseases, while fulfilling its important responsibility to assure that the products are safe and effective for these highly vulnerable populations. There are numerous examples of drugs approved for treating rare diseases where FDA’s flexibility and sensitivity to the obstacles of drug development for rare diseases has brought forth a successful treatment. Many of the 357 approved orphan drugs have been successfully tested on extremely limited numbers of patients, serving as a testament to FDA’s commitment to these patients. This is possible when the best science is flexibly applied and when therapies are truly effective. Successful examples include:

- Carbaglu (carglumic acid) for the treatment of NAGS deficiency, the rarest of the Urea Cycle Disorders (UCDs) — This disease affects fewer than 10 patients in U.S. at any given time and fewer than 50 patients worldwide. This drug was approved in March

2010 based on a case series derived from fewer than 20 patients and comparison to a historical control group.

- VPRIV (velaglucerase) for the treatment of Gaucher disease, a rare genetic disorder — This disease affects approximately 2,000 people in the U.S. and approximately 5,000 worldwide. This drug was approved in February 2010 based on a development program that included about 100 patients and a pivotal study of 25 patients.
- Myozyme (alglucosidase alfa) for the treatment of the infantile variant, and rapidly fatal, form of Gaucher disease — The variant of this disease affects about 1,000 patients in the U.S. and about 3,000 patients worldwide. This drug was approved in April 2006 based on a clinical development program of fewer than 80 patients and a pivotal study that included 18 patients.
- Ceprotin (human plasma derived protein C concentrate) for the treatment of severe congenital Protein C deficiency — There are fewer than 20 known patients with this disorder in the United States. This biologic drug product was approved in March 2007 based on a study of 18 patients using comparison to historical control data.

## **FDA RARE AND NEGLECTED DISEASES REVIEW GROUPS**

While there have been many successes in the development of products for rare and neglected diseases, because of the remaining needs and great interest on the part of multiple stakeholders, it is timely to examine what more may be possible. With the support of Senator Brownback,

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) directs 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. The Rare Disease Review Group includes 24 expert FDA staff scientists from a broad array of pre-clinical and clinical disciplines. They've been asked to consider how FDA currently evaluates drugs, biologics and medical devices for treating rare diseases and how that process can be optimized. The neglected disease review group is composed of experts in infectious diseases from all FDA medical product Centers and the Office of the Commissioner. This group is reviewing present FDA guidance and the different local and international programs that encourage development of medical products for these diseases and, similarly, will identify opportunities to enhance Agency efforts.

These review groups are already active and on track in evaluating current activities and plan to recommend to the FDA Commissioner potential options to further support and facilitate the development and evaluation of medical products to prevent, diagnose, and treat rare diseases and neglected diseases of the developing world.

FDA believes public input to be very important in this evaluation and will also be holding meetings for that purpose. A meeting on rare diseases is scheduled for June 29 and 30, 2010, and 26 speakers are already signed up to provide comments. Another Part 15 hearing, to allow

FDA to seek public input on the challenges and possible solutions encouraging development of products for neglected diseases, is planned for September. Finally, FDA and NIH are co-sponsoring an Institute of Medicine (IOM) study, begun 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.

Based on the Working Groups' deliberations, and the input we receive from stakeholders, I look forward to issuing a report to Congress, as well as development and issuance of guidance, and taking whatever further steps are feasible to enhance these programs.

## **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 applied product development and evaluation research, a gap that is reflected in the lack of real products getting to patients for many such diseases, despite advances in basic sciences. FDA's regulatory science research helps bridge this gap and facilitates development and availability of safe and effective products to meet public health needs.

Regulatory science is the development of tools, methods, assays, standards, and models that help speed and improve the development, review, and approval of innovative products. These tools, and better evaluation methods, are particularly critical for facilitating development of products for which commercial incentives may be weak or uncertain, or where scientific complexities in

evaluating product effectiveness are major challenges. Examples relevant to our hearing today include the need for better, faster ways, including biomarkers and novel clinical trial designs, to predict and monitor effectiveness of treatments both for rare diseases and for many neglected diseases, such as TB.

FDA's FY 2011 budget includes dedicated funding for FDA to strengthen its critical scientific infrastructure and capacity to leverage the opportunities provided by 21<sup>st</sup> century science and to enhance its scientific collaborations. Through collaboration, FDA will foster new opportunities for patients and consumers. One recent example of a collaborative success involved the work of FDA biochemists work to help improve a complex vaccine manufacturing process and making the information available to collaborators engaged with PATH, a major international non-profit organization, in developing new meningitis vaccines for the developing world.

Continued investments in regulatory science will allow FDA to develop standards for products employing new and emerging technologies, modernize the standards for evaluating existing products, and accelerate the development of essential medical therapies, while at the same time assuring the new products are safe and effective. FDA's regulatory science seeks to improve efficiency of clinical trials, speed product development, and reduce attrition rates of products under development. 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.

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 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 rare and neglected diseases.

### **Tuberculosis – A Case Study**

The World Health Organization estimates that one in three people in the world is infected with latent, or dormant, tuberculosis bacteria that can become active as a result of a weakened or senescent immune system. Today, there are no simple, rapid and accurate tests to diagnose tuberculosis. This gap impedes timely detection and treatment of this contagious, and too often deadly, infectious disease.

The conference report for the FY 2010 Appropriations Act directs that not less than \$6,000,000 be used for FDA Critical Path Partnerships. \$2,000,000 of this appropriation is to support research partnerships encouraging the development of treatments or rapid diagnostic tests for tropical diseases, with an emphasis on tuberculosis.

On June 7 and 8, FDA hosted a TB diagnostics workshop, in collaboration with the CDC and NIH. The workshop identified scientific gaps in the TB diagnostic armamentarium, opportunities to harness new technologies, and the feasibility of prospectively collecting specimens from patients participating in TB trials to support the development of new diagnostic

tests. The workshop was attended by approximately 150 registrants from government, academia, industry, and non-profit organizations, both from the U.S. and overseas. The workshop laid the groundwork for interagency collaboration on programs for developing TB diagnostic tests and for establishing a repository of specimens from participants in TB clinical trials. This repository may serve to identify biomarkers that can expedite future clinical trials.

FDA established a TB cross-center working group to recommend priority areas for TB medical product development. As a result of this effort, FDA will soon publish a request for applications (RFA) soliciting proposals from outside scientists for collaborative initiatives to address areas of need in the treatment, diagnosis, and prevention of TB and other tropical diseases.

FDA is also collaborating with the Clinical Data Interchange Standards Consortium (CDISC). This consortium is working to develop uniform data collection standards to be used in clinical trials for tuberculosis. This type of collaborative effort is critical to facilitate the collection of standardized clinical data and expedite TB drug development.

## **FDA COLLABORATION WITH THE WORLD HEALTH ORGANIZATION (WHO) ON VACCINES FOR RARE AND NEGLECTED DISEASES**

FDA recognizes the tremendous unmet need to engage globally in an effort to assist other regions and nations in assessing vaccines for approval by their governments and in helping to ensure their quality and safety. Further, FDA recognizes the need to develop new innovative regulatory pathways for candidate vaccines for global diseases to reach developing countries.

FDA has traditionally worked with manufacturers to approve vaccines for the U.S. population. However, new paradigms of vaccine development supported by the Gates Foundation and other initiatives, along with an increase in regulatory submissions to FDA for global vaccines – to prevent or treat diseases often endemic outside the U.S. – have provided an impetus for the development of new regulatory strategies at FDA. In 2008, FDA issued guidance on the development of vaccines to protect against global infectious diseases. The guidance was extremely well received by the global health community.

A core component of FDA’s efforts in this regard is its commitment to support and complement the efforts of the World Health Organization (WHO). FDA’s contribution to the WHO vaccine quality and safety goals is long-standing and was formalized in 1998 with its designation as a Pan American Health Organization (PAHO)/WHO Collaborating Center for Biological Standardization. In recent years, FDA’s support has grown beyond the routine collaboration of providing expert input to WHO consultations and laboratory collaborations for international reference standards. FDA now is an active partner with the WHO in its vaccine prequalification program and its efforts to build regulatory capacity in developing countries.

### **The WHO Vaccine Prequalification Program**

The vaccine prequalification program is a service provided by WHO to United Nations (UN) agencies that purchase vaccines, providing independent guidance and advice to the UN on the quality, safety, and efficacy of vaccines being considered for purchase. This assistance helps to ensure that each vaccine under consideration is suitable for target populations and complies with established standards of quality. In 2007, WHO designated FDA as a “reference” national regulatory authority (NRA) for WHO prequalified vaccines. In 2008, FDA and WHO signed

confidentiality agreements specific to communications that would be undertaken in the context of the WHO vaccine prequalification process. Currently, CBER is the reference NRA for a total of seven U.S. licensed vaccines.<sup>1</sup>

### **Building the Requisite Regulatory Capacity in the Developing World**

CBER provides support to several WHO regional vaccine networks to enhance scientific and regulatory capacity needed to assure the development of high quality vaccines. Specifically, CBER actively engages with the WHO Developing Country Vaccine Regulator Network (DCVRN), a WHO-funded network of NRAs from Brazil, China, Cuba, South Korea, India, Indonesia, the Russian Federation, South Africa, and Thailand. The DCVRN builds regulatory capacity among vaccine-producing developing countries through information sharing, training, and mentoring activities. Representatives from member DCVRN countries meet on a biannual basis to gain timely information from independent experts and developers on specific issues relating to vaccine trials occurring in developing countries and to develop institutional plans and other activities that aim to strengthen regulatory capacity.

CBER also provides expert input to the WHO African Vaccine Regulatory Forum (AVAREF). WHO coordinates this forum in conjunction with the WHO African Regional Office to assist in defining the role of NRAs of African nations in regulating clinical trials of vaccines, in interactions with national and local IRBs and ethical committees and in strengthening the capacity of the NRAs to regulate new products. In this capacity, FDA participates as expert

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<sup>1</sup> Rotavirus Vaccine, Live, Oral, Pentavalent (Tradename: RotaTeq®); Prequalified Oct 7, 2008; Influenza Virus Vaccine (Tradename: Fluvirin®); Prequalified Dec 4, 2009; Influenza A (H1N1) 2009 Monovalent (No tradename; Manufacturer: Novartis Vaccines and Diagnostics Limited), Prequalified by WHO Dec 9, 2009; Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM<sub>197</sub> Protein)(Tradename: Prevnar®), Prequalified by WHO Dec 28, 2009; Influenza Virus Vaccine (Tradename: Fluzone®), Prequalified Jan 21, 2010; Influenza A (H1N1) 2009 Monovalent (No tradename; Manufacturer: Sanofi Pasteur, Inc.), Prequalified Jan 27, 2010; Influenza A (H1N1) 2009 monovalent (No tradename; Manufacturer: MedImmune LLC), Prequalified Feb 25, 2010.

advisors, in particular sharing the regulatory mechanisms used to evaluate the safety and efficacy of investigative products.

## **CONCLUSION**

FDA is fully committed to doing all we can to help facilitate the availability of safe and effective therapies to patients in need. FDA has an ongoing broad range of vibrant programs to facilitate the development and improve access to medical products to treat and prevent rare and neglected diseases, and these activities have helped benefit people in our country and globally. Advances in regulatory science offer tremendous promise to improve product evaluation and translation of advances in basic science to products that can benefit people in the U.S. and globally. Thank you again for this opportunity to discuss rare and neglected diseases. I welcome your comments and questions.

**Jesse L. Goodman, M.D., M.P.H.**

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Dr. Goodman became Chief Scientist and Deputy Commissioner for Science and Public Health of FDA in 2009. He has broad responsibility for and engagement in leadership and coordination of FDA's cross-cutting scientific and public health efforts.

From 2003-2009, Dr. Goodman was Director of FDA's Center for Biologics Evaluation and Research (CBER), which oversees medical and public health activities critical to U.S. and global preparedness and the development, evaluation, safety, quality and availability of biologics.

A graduate of Harvard, Dr. Goodman received his M.D. from the Albert Einstein College of Medicine and did residency and fellowship training at the Hospital of the University of Pennsylvania and at UCLA where he was also Chief Medical Resident. Prior to joining FDA, he was Professor of Medicine and Chief of Infectious Diseases at the University of Minnesota, where he directed the multi-hospital Infectious Diseases research, training and clinical programs, and where his NIH funded laboratory first isolated and characterized *Anaplasma phagocytophilum*, the infectious agent causing a new tick borne disease, human granulocytic ehrlichiosis.

Dr. Goodman has authored numerous scientific papers and edited the book, "Tick Borne Diseases of Humans," published by ASM Press in 2005. Dr. Goodman has been elected to the American Society for Clinical Investigation and to the Institute of Medicine of the National Academy of Sciences, where he is a longstanding member of the Forum on Emerging Threats. He is an active clinician and teacher who is Board Certified in Internal Medicine, Oncology and Infectious Diseases and is Staff Physician and Infectious Diseases Consultant at the National Naval and Walter Reed Army Medical Centers. Dr. Goodman is Adjunct Professor of Medicine at the University of Minnesota.