Report to Congress

Improving the Prevention, Diagnosis, and Treatment of Rare and Neglected Diseases

In Response to

Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act, 2010, Public Law 111-80, Section 740

Department of Health and Human Services
Food and Drug Administration
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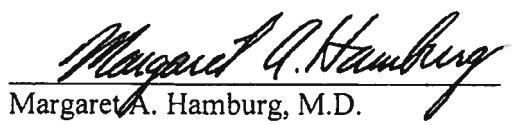

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TABLE OF CONTENTS

Improving the Prevention, Diagnosis, and Treatment of Rare and Neglected Diseases

INTRODUCTION

Section 740 of the fiscal year (FY) 2010 Appropriation Act (Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriation Act, 2010, Public Law 111-80), dated October 21, 2009, required the Commissioner, Food and Drug Administration (FDA), to establish two review groups within FDA to make recommendations to the FDA Commissioner on appropriate preclinical, trial design, and regulatory paradigms and optimal solutions to prevent, diagnose, and treat (1) rare diseases and (2) neglected diseases of the developing world. Section 740 requires these groups to submit a report to Congress that describes their findings and recommendations. The language in section 740 of the Appropriation Act follows:

> *740. (a) The Commissioner of Food and Drugs shall establish within the Food and Drug Administration a review group which shall recommend to the Commissioner of Food and Drugs appropriate preclinical, trial design, and regulatory paradigms and optimal solutions for the prevention, diagnosis, and treatment of rare diseases: Provided, That the Commissioner of Food and Drugs shall appoint individuals employed by the Food and Drug Administration to serve on the review group: Provided further, That members of the review group shall have specific expertise relating to the development of articles for use in the prevention, diagnosis, or treatment of rare diseases, including specific expertise in developing or carrying out clinical trials.*
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> *(b) The Commissioner of Food and Drugs shall establish within the Food and Drug Administration a review group which shall recommend to the Commissioner of Food and Drugs appropriate preclinical, trial design, and regulatory paradigms and optimal solutions for the prevention, diagnosis, and treatment of neglected diseases of the developing world: Provided, That the Commissioner of Food and Drugs shall appoint individuals employed by the Food and Drug Administration to serve on the review group: Provided further, That members of the review group shall have specific expertise relating to the development of articles for use in the prevention, diagnosis, or treatment of neglected diseases of the developing world, including specific expertise in developing or carrying out clinical trials: Provided further, That for the purposes of this section the term ''neglected disease of the developing world'' means a tropical disease, as defined in section 524(a)(3) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360n(a)(3))*
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> *(c) The Commissioner of Food and Drugs shall— (1) submit, not later than 1 year after the date of the establishment of review groups under subsections (a) and (b), a report to Congress that describes both the findings and recommendations made by the review groups under subsections (a) and (b); (2) issue, not later than 180 days after submission of the report to Congress under*

paragraph (1), guidance based on such recommendations for articles for use in the prevention, diagnosis, and treatment of rare diseases and for such uses in neglected diseases of the developing world; and (3) develop, not later than 180 days after submission of the report to Congress under paragraph (1), internal review standards based on such recommendations for articles for use in the prevention, diagnosis, and treatment of rare diseases and for such uses in neglected diseases of the developing world.

This report on rare diseases and neglected diseases responds to section 740 of the 2010 Appropriation Act and presents the findings and recommendations of the Rare Diseases Group and the Neglected Diseases Group.

I. REPORT FROM THE RARE DISEASES GROUP

A *rare disease* is any disease or condition that affects fewer than 200,000 people in the United States[1]. Most rare diseases are genetic. Many rare diseases appear early in life. A rare disease is also known as an *orphan disease* because many manufacturers do not take an interest in developing medical products for such small populations. In response to Section 740 of the Appropriations Act of 2010,[2] the Rare Diseases Group (RDG) undertook a number of activities to gather input on and assess practices and concerns related to the regulation of medical products, including drugs, biological[3] products, and medical devices for rare diseases (i.e., to prevent, diagnose, and treat or manage rare diseases).

The RDG reviewed FDA practices for regulating these medical products and evaluated existing regulations and policies regarding medical products for rare diseases of the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiologic Health (CDRH).

On June 29 and 30, 2010, FDA held a public hearing to gather input from interested stakeholders on issues related to the Agency's regulation of medical products for rare diseases. The goal of the public hearing was to gain insights and recommendations from health care providers, academia, industry, patients, and other interested persons on their perspectives on various aspects of the development and regulation of medical products for rare diseases.[4]

FDA's Office of Orphan Products Development (OOPD) and the National Institutes of Health (NIH) Office of Rare Diseases Research (ORDR) commissioned an Institute of Medicine (IOM) committee to assess existing strategies to promote research discoveries and development of orphan products to improve the health of people with rare diseases. The resulting report from the committee, *Rare Diseases and Orphan Products: Accelerating Research and Development,* was published in October 2010.[5] The RDG carefully considered the IOM recommendations directed to FDA in its role in facilitating development, evaluating, and approving medical products for rare diseases.

Based on the RDG's deliberations and after careful consideration of comments and recommendations from the public hearing and the IOM committee's recommendations, the RDG developed findings and recommendations to improve practices that could

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[1] Rare Disease Act of 2002.

[2] Public Law 111-80, October 21, 2009.

[3] Drugs and biological drug products will be referred to collectively as *drugs* unless otherwise specified; devices and biological device products will be referred to collectively as *devices* unless otherwise specified.

[4] A transcript of the meeting, including public recommendations, is available on the Critical Path Initiative website under Resources for You; see www.fda.gov/CriticalPath.

[5] The IOM report is available at http://iom.edu/Reports/2010/Rare-Diseases-and-Orphan-Products-Accelerating-Research-and-Development.aspx.

further facilitate the development of medical products for rare diseases. The findings and recommendations are discussed here.

A. Findings

The RDG identified both strengths and constraints in the current paradigm for drug and device regulation. An evaluation of current agency practices revealed that extant regulations provide the flexibility needed for the review of medical products for the diagnosis, treatment, and prevention of rare diseases.[6] FDA recognizes that, for all serious and life-threatening diseases, greater drug safety risks may be justified when the potential benefits of the drug are seen in the essential aspects of the disease and outweigh these risks. The approval standard for drugs and biologic medical products of "substantial evidence of effectiveness" and safety[7] remains an appropriate one for rare diseases. In devices, the approval standard for a humanitarian device exemption (HDE) of reasonable assurance of safety and probable benefit is also appropriate.[8] Current regulations allow for flexibility and scientific judgment[9] when applying the standard in assessing the totality of the evidence. FDA has successfully applied this flexibility to approve therapeutics for rare genetic diseases (e.g., Huntington's disease) and rare cancers, among others (see Appendix 1, which lists several examples of medical products that have been approved, licensed, or cleared for rare diseases).

Additionally, FDA makes best use of existing regulatory provisions to facilitate efficient drug development and availability of drugs to patients during the investigational period. These regulatory provisions include:

- Fast Track and Accelerated Approval processes intended to facilitate the development and review of medical products for serious and life-threatening conditions[10]
- Priority review[11] of applications for medical products "used to treat serious diseases, or for less serious diseases with the potential to provide significant advances in treatment" (PDUFA 1992)
- Expanded Access of patients to investigational products,[12] allowing for use in:

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[6] See 21 CFR part 314 (drugs), 21 CFR part 601 (biologics) and 21 CFR part 814 (devices).
[7] 21 CFR 314.125 and 314.126
[8] 21 CFR 814.100
[9] See e.g., 21 CFR 314.105
[10] 21 CFR 314.500-560, 21 CFR 601.40-46, http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/ucm128291.htm#fast; or http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079736.pdf
[11] http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/ucm128291.htm#priorityreview
[12] See, e.g., for drugs 21 CFR 312.300-320 and http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm172492.htm; 21 CFR 812.36 for devices.

- Individual patients, including emergency use
- Intermediate-sized patient populations
- Treatment investigational new drug (IND) or treatment protocols

Despite FDA's many strengths, including experienced review staff, there are clear areas for potential improvement. Recent activities to advance understanding of the need for and approach to developing and regulating therapies for rare diseases, both within FDA and in organizations outside FDA, are expected to facilitate development and to confer significant medical and health care benefits in coming years. Examples of areas of ongoing activities include:

- Examining and evaluating policy and procedures for the regulation of medical products for rare diseases. For example, FDA is interested in helping to further the development and understanding of new clinical trial designs and statistical methods that are being proposed and evaluated by the clinical investigation community, particularly in academic institution centers. FDA has published guidance on some aspects of these methods (e.g., adaptive designs and Bayesian methods) and participates in public conferences and workshops to advance these areas.
- Developing education and training programs for FDA rare disease reviewers and external stakeholders. For example, FDA developed an annual rare disease-specific training course for all FDA review staff. During 2011, FDA conducted this training course for drug reviewers between February 17 and April 7. FDA also launched an annual Science of Small Clinical Trials Course for FDA staff and for external participants.[13]
- Increasing communication efforts involving rare diseases to stakeholders within the Federal government and outside FDA, as well as academia and the research community, industry, professional associations, and advocacy organizations. For example, FDA staff are consulting with the staff of the NIH Therapeutics for Rare and Neglected Diseases program to identify areas where meeting the two agencies' responsibilities can be coordinated and to provide mutual support for each agency's efforts to advance therapeutics for rare diseases.

The RDG noted that efforts to develop medical products for rare diseases have increased substantially in recent years and are expected to increase, given advances in molecular biology, bioengineering, computational modeling, and targeted pharmaceutical and biotechnology product development.

Impediments to progress in the therapeutic armamentarium against rare diseases include the often inadequate scientific foundation and core knowledge vital to support medical product development for rare diseases, limited regulatory precedents for most of the

[13] FDA first offered the training course on the Science of Small Clinical Trials in January 2009. The course was revised and improved during 2010, and FDA opened the course to external participants. The course was further improved for 2011, and FDA will conduct this course during April and May of 2011.

individual diseases and some of the most technologically innovative products in development, and suboptimal collaboration among relevant stakeholders.

The constraints identified by the RDG represent opportunities for continued improvement.

B. Summary of Recommendations

The RDG identified key areas where additional efforts may enable significant advances to prevent, diagnose, and treat rare diseases. Recommendations are organized under the key areas — some of the recommendations may be more effectively implemented through collaborations with other members of the medical product development community.

> (1) increase biomedical and regulatory scientific development for rare diseases, (2) increase collaboration of rare disease stakeholders both within and outside FDA, (3) conduct a thorough review of the development and regulatory history of orphan drug products to help identify effective development approaches.

Key Area: increase the foundation of biomedical and regulatory science required to support development and regulatory assessment of medical products for rare diseases.

1. Conduct disease-specific natural history studies and develop databases. A thorough understanding of the natural history of a rare disease is essential for rational and efficient development of medical products for rare diseases. An initiative to systematically gather the natural history data to support clinical development in rare diseases would be invaluable, and FDA believes that many academicians, advocacy groups, and patients would be interested in collecting such data. Infrastructure support, however, may be needed for these efforts to occur and has been difficult for investigators to secure. Parties that conduct such studies would greatly benefit from close collaboration with FDA to obtain advice on the design of the most appropriate natural history studies to support the multiple needs of therapeutic development programs and ultimately meet regulatory requirements.
2. Identify, develop, and qualify novel biomarkers (where applicable). Biomarkers are molecules or other measurable biological factors found in blood, body fluids, or tissues that serve as markers of a disease or condition and can be used to assess an individual's medical and diagnostic status during and after treatment. Biomarkers that are well-understood have the potential to substantially improve and speed drug and device development because they can serve as markers of prognosis and of treatment response. Research into each disease to identify and then develop sufficient evidence to support reliance on biomarkers as predictors

of effectiveness, safety, or other aspects of clinical development could markedly advance prevention, diagnosis and treatment of rare diseases.

3. Explore the use of novel clinical trial designs and statistical methods for rare disease development programs.

Key Area: Increase collaboration among rare disease stakeholders both within and outside FDA. For example, FDA has established the Biomarker Qualification Process[14] as a structured approach for working with outside consortia seeking to establish a novel biomarker for a specific use in drug development (termed a "context of use") and helping them develop the information needed to justify a conclusion that a biomarker is *qualified* for use in regulatory decision-making in a specified manner. Other examples of collaboration efforts could include enhanced FDA participation at scientific meetings and workshops, developing FDA guidances or other advice, and creating focused teams to address specific areas that would contribute to advancing rare disease medical product development.

Key Area: Gain a thorough understanding of the regulatory history of orphan drug products to help identify effective development approaches, particularly for addressing the uncertainties of biomedical knowledge along the product development pathway, so that patterns can be adapted to future development programs.

1. Perform a detailed analysis of FDA's 27-year history of Orphan drug approvals to identify factors and methods that have led to successful drug development and approval or have impeded development and identify areas for improvement. This comprehensive assessment may also identify scientific issues that have posed the greatest difficulties for drug and device developers and approaches that have been effective in overcoming these difficulties.
2. In the case of medical devices, FDA plans to analyze the reasoning presented in device applications for requesting a humanitarian device exemption (HDE) as well as why an application was successful or not with the goal of identifying areas for improvement.
3. Undertake a broad assessment of the barriers to, and meaningful incentives for, the development of medical devices for rare diseases.

The above key areas contain opportunities that are not solely regulatory in scope and that should be part of a larger drug and device industry focus on products for rare diseases. These recommendations are intended to affect the drug and device development process, and it is critical that FDA play a prominent role in these efforts with other appropriate organizations.

[14] http://inside.fda.gov:9003/CDER/OfficeofTranslationalSciences/BiomarkerQualifications/default.htm

C. Conclusions

The RDG has identified current strengths and opportunities for improving regulatory paradigms in ways that will facilitate development of medical products for rare diseases. Strengths include the existence of an established history of thoughtful and flexible rare disease medical product regulation and approval that has delivered substantial benefits to patients with rare diseases. FDA also points out that strengthening the scientific foundation that forms the basis for FDA's regulatory process and enhancing collaborations among stakeholders would greatly improve overall rare disease medical product development processes.

II. REPORT FROM THE NEGLECTED TROPICAL DISEASES GROUP

"Neglected diseases of the developing world" are generally infectious diseases that are rare or absent in developed countries, but often are very widespread in the developing world. Most neglected diseases occur in tropical climates and these diseases will be referred to in this report as "neglected tropical diseases" (NTDs). Many NTDs are transmitted by insects or contaminated food and water in parts of the world with poor sanitation and hygiene.

Non-pharmacological interventions such as clean water supplies and the use of bed netting play an important role in the preventing NTDs. Although FDA approval of medical products is not required for their use in other countries, many of these countries have limited regulatory capacities and may rely on FDA or other regulatory authorities to assess product safety, efficacy, and quality. As part of the NTD group's assessment of concerns and issues related to developing, evaluating, and approving medical products for NTDs, the NTD group evaluated current and planned activities that will help improve the development of medical products for NTDs.

On September 23, 2010, FDA sponsored a public hearing to solicit the perspectives of the public and interested health-related organizations on issues and concerns related to the development of medical products for NTDs.[15] During the public hearing, a number of recommendations were made.

Based on its assessment of ongoing and planned activities and after careful consideration of the input and recommendations received at the public hearing, the NTD group made the following findings and recommendations.

[15] A transcript of the meeting, including public recommendations, is available on the Critical Path Initiative website under Resources for You. See www.fda.gov/CriticalPath.

A. Findings

The NTD group found that appropriate regulatory paradigms are in place through FDA's existing programs and activities related to FDA review of marketing applications for products for NTDs. FDA has approved, licensed, or cleared a number of products for NTDs (see Appendix 2 for a list of products). FDA's Office of International Programs has existing outreach activities related to NTD product development. Nevertheless, the NTD group found that enhancing efforts, including those in Federal, academic, and other collaborative programs, could help strengthen certain basic and applied research areas (e.g., regulatory science), that form the foundation for medical product development and the basis of regulatory review and assessment. The NTD group also found that enhancing the clinical trials infrastructure, through clinical trials consortia or other organizations, could facilitate the conduct of trials in countries of the developing world where NTDs mostly occur.

B. Summary of Recommendations

The review group identified the following recommendations for improving the development of medical products for NTDs. The four recommendations listed below are related directly to FDA review work and are currently underway or being planned by FDA. The NTD group believes that these recommendations will positively affect the development of products for NTDs.

Recommendation 1. Issue guidance documents containing information on drug development and review standards for the following NTD-related areas:

- Development of drugs[16] for treating NTDs
- Development of drugs for treatment of pulmonary tuberculosis
- Development of investigational drugs used in combination[17]

Recommendation 2. Revise the CBER guidance *General Principles for the Development of Vaccines to Protect Against Global Infectious Diseases*

Recommendation 3. Hold CDRH Expert Panel meeting to discuss issues concerning FDA regulation of diagnostic tests for pulmonary tuberculosis

Recommendation 4. Issue a guidance document on the regulation of diagnostic tests for pulmonary tuberculosis

[16] All references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[17] The draft guidance *Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination* was issued on December 14, 2010 and is available on FDA's website.

One other consideration is to explore extending FDA's Orphan Drug Grants Program to include grants for studies of diagnostic tests or other devices for NTDs.

In addition to the previously mentioned recommendations, strengthening the scientific foundation that forms the basis of drug development and FDA's regulatory process would greatly improve overall development process for NTD products. Most of these activities are conducted outside of FDA's purview, but are included in this report because of their importance in enhancing successful NTD product development.

These activities include, for example, basic and applied NTD research by the National Institutes of Health, academia, or other consortia. Examples of basic and applied research areas that are particularly helpful include:

- programs to perform nonclinical studies to characterize preliminary safety of NTD products to be brought forward into clinical development

- development of animal models to characterize a product's potential activity in the prevention or treatment of NTDs

- clinical studies to characterize suitable endpoints to evaluate the efficacy of products for preventing and treating NTDs

- establishing, maintaining and making biorepositories available with clinical samples from patients with NTDs to streamline the clinical evaluation process for new diagnostics

C. Conclusions

The NTD group found that appropriate regulatory paradigms are, for the most part, already in place through FDA's existing programs and activities related to medical products for NTDs. However, more can be done. The NTD group makes several recommendations specific to FDA. The NTD review also highlights some important activities performed by other Federal agencies, academia, or consortia that are also important for successful NTD product development.

APPENDIX 1: Examples of Medical Products Approved for Rare Diseases

Table 1: Examples of regulatory flexibility applied to drug and biological product approvals by FDA for rare disease indications

Drug and Rare Disease Indication	Special Consideration for the Rare Disease Circumstance
Inactivated Japanese encephalitis virus vaccine (Ixiaro) for the prevention of Japanese encephalitis.	Approval was based on evidence of effect on a surrogate endpoint.
Human fibrinogen concentrate (RiaSTap) for the treatment of congenital fibrinogen deficiency.	Accelerated Approval was based on clinical experience in Europe and evidence of an effect on a surrogate endpoint.
Tetrabenazine (Xenazine) for the treatment of chorea associated with Huntington's disease.	Approval based primarily on the results of a single study.
Agalsidase beta (Fabrazyme) for the treatment of Fabry disease.	Accelerated Approval based on the results of a single study and on the drug's effect on a surrogate endpoint.
Imatinib mesylate (Gleevec) for the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors (GIST).	Accelerated Approval based on the results of a single study and the drug's effect on a surrogate endpoint. Subsequently a conventional approval was granted for treatment of a variety of rare tumors known to express one of the molecular targets inhibited by imatinib, based on the results of one multi-disease open-label phase 2 trial without a comparator arm and on published case reports.
Alglucosidase alfa (Myozyme) for the treatment of Pompe disease.	Approval was based on the results of a single, historically controlled study.

Table 2: Examples of devices approved by CDRH for rare diseases

Device Name and Type	Proposed Use/Indication
Melody Transcatheter Pulmonary Valve (TPV)	The Melody TPV is used in patients to restore pulmonary valve function for patients who experience failed pulmonary valve conduits. Technical Information: The Melody TPV is used as an adjunct to surgery to manage pediatric and adult patients with the following clinical conditions: 1) Existence of a full (circumferential) Right Ventricular Outflow Tract (RVOT) conduit that was equal to or greater than 16 mm in diameter when originally implanted **and** 2) Dysfunctional RVOT conduits with a clinical indication for intervention, and either: Regurgitation:≥moderate regurgitation, or Stenosis: mean RVOT gradient > 35 mmHg.
NeuRx RA/4 Respiratory Stimulation System	The NeuRx RA/4 is a pacing device that helps patients with a paralyzed diaphragm breathe without a ventilator for up to four hours. Technical Information: The NeuRx RA/4 is indicated for use in patients, aged 18 years or older, with stable, high spinal cord injuries with stimulatable diaphragms, but lack control of their diaphragms.
Fujirebio Mesomark™ Assay - monitors the condition of patients diagnosed with forms of mesothelioma	Mesothelioma is a rare form of cancer. The assay measures the amount of a specific biomarker in the blood of mesothelioma patients to assist physicians monitor patients to assess their response to treatment. Technical Information: The Fujirebio Mesomark™ Assay is an Enzyme Linked Immunosorbent Assay (ELISA) for the quantitative measurement of Soluble Mesothelin Related Peptides (SMRP) in human serum. Measurement of SMRP may aid in the monitoring of patients diagnosed with epitheloid or biphasic mesothelioma.
Vertical Expandable Prosthetic Titanium Rib (VEPTR)	This device can be adjusted as a child grows. Technical Information: The VEPTR is used to treat Thoracic Insufficiency Syndrome (TIS), which is defined as the inability of the thorax to support breathing or lung growth in skeletally immature patients.
Debakey VAD Heart Pump for Children	The DeBakey VAD® Child is a miniaturized heart pump designed to help the left ventricle of the heart pump blood. It is intended for use in children 5 to 16 years old who are awaiting a heart transplant. Technical Information: The DeBakey VAD® Child is designed to provide temporary left side mechanical circulatory support as a bridge to cardiac transplantation for pediatric patients (5-16 years old, with BSA > 0.7 m2 and < 1.5 m2) who are in NYHA Class IV end stage heart failure, are refractory to medical therapy, and who are (listed) candidates for cardiac transplantation.
Contegra® Pulmonary	The Contegra® Pulmonary Valved Conduit is a bioprosthetic (prosthesis made from biological material) heart valve made from a segment of cow (bovine) jugular vein.

Valved Conduit, Models 200 (unsupported) and 200S (supported) to replace a defective pulmonary valve	The vein contains a venous valve with three leaflets that open to allow the forward flow of blood and close to prevent the backward flow of blood. Technical Information: The Contegra® Pulmonary Valved Conduit is used for Correction or reconstruction of RVOT in: pulmonary stenosis, TOF, truncus arteriosus, transposition w/ ventricular septal defect (VSD), pulmonary atresia; and for replacement of previously implanted but dysfunctional pulmonary homografts or valved conduits, in children and young adults under 18 years of age.
TAS Ecarin Clotting Time Test	The TAS Ecarin clotting time test is a laboratory test used to monitor clotting of the blood in patients being treated with hirudin, a clot preventing medication. Technical Information: To be used to determine the anticoagulant effect of recombinant hirudin (r-hirudin) during cardiopulmonary bypass in patients who have heparin induced thrombocytopenia (HIT).
Enterra™ Therapy System stomach stimulation system	Gastroparesis is a condition that reduces the ability of the stomach to empty its contents. The device is an electrical stimulation system implanted on the stomach to treat long term nausea and vomiting that results from the inability of the stomach to empty its contents when drugs alone do not help. Technical Information: For the treatment of chronic, intractable (drug refractory) nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology.

APPENDIX 2: FDA-Approved, Cleared, or Licensed Medical Products For NTDs

The tropical diseases in this table are taken from section 524(a)(3) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360n(a)(3)). The listed drugs have FDA-approved indications for treating the corresponding pathogen.

Tropical Disease	FDA-Approved Drugs	
Tuberculosis	capreomycin cycloserine ethambutol ethionamide isoniazid (INH) pyrazinamide (Pyr)	rifampin (R) rifapentine streptomycin Rifamate® (fixed-dose INH, R) Rifater® (fixed-dose INH, R, Pyr)
Malaria	chloroquine doxycycline (prophylaxis) mefloquine primaquine pyrimethamine	quinidine gluconate quinine Coartem® (artemether-lumefantrine) Fansidar® (pyrimethamine-sulfadoxine) Malarone® (atovaquone-proguanil)
Blinding trachoma	doxycycline erythromycin minocycline	tetracycline demeclocycline
Buruli Ulcer	There are no FDA-approved drugs for this indication	
Cholera	doxycycline minocycline	tetracycline demeclocycline
Dengue/dengue hemorrhagic fever	There are no FDA-approved drugs for this indication	
Dracunculiasis (guinea-worm disease)	There are no FDA-approved drugs for this indication	
Fascioliasis	There are no FDA-approved drugs for this indication	
Human African trypanosomiasis	eflornithine**	
Leishmaniasis	amphotericin B liposomal amphotericin B	
Leprosy***	clofazimine** dapsone	
Lymphatic filariasis	diethylcarbamazine**	
Onchocerciasis	ivermectin diethylcarbamazine**	
Schistosomiasis	Praziquantel	
Soil-transmitted helminths	Mebendazole	
Yaws	doxycycline minocycline penicillin G	tetracycline demeclocycline

** These drugs are no longer marketed in the United States.

*** Thalidomide is approved for the treatment of erythema nodosum leprosum – an inflammatory complication of treatment of leprosy.

Neglected Tropical Disease	FDA Cleared or Approved Diagnostic Tests
Tuberculosis	There are several FDA-cleared or approved tests for tuberculosis including liquid media-based culture systems, a nucleic acid amplification test for the detection *of M. tuberculosis* complex directly from sputum, and tuberculin skin tests (PPD)/interferon gamma releasing assays (IGRAS) for diagnosing latent tuberculosis infection. One HPLC system has been FDA-cleared for identification of *M. tuberculosis* from cultured isolates.
Malaria	There are two FDA-cleared tests for malaria, one as an aid for staining blood specimens and the more recently cleared BinaxNOW Malaria Rapid Antigen Test. The latter is the first rapid antigen test for malaria cleared by FDA and an important diagnostic advance.
Blinding Trachoma	There are no FDA-cleared or approved tests specifically for trachoma; however, there are FDA-cleared devices for *Chlamydia trachomatis* genital infection, including direct antigen detection, nucleic acid amplification assays, hybridization assays, serum ELISA, etc.
Buruli Ulcer	None.
Cholera	FDA has cleared several rapid ELISA-based tests specific for *V. cholerae O1*, including a lateral-flow colorimetric test, the Cholera SMART II.
Dengue/dengue hemorrhagic fever	None. However, several diagnostic tests are anticipated to be available in 2011.
Dracunculiasis (guinea-worm disease)	None
Fascioliasis	None
Human African trypanosomiasis	None
Leishmaniasis	There are two FDA-cleared assays for Leishmania although only one is marketed, the Kalazar Detect.
Leprosy	None
Lymphatic filariasis	None
Onchocerciasis	None
Schistosomiasis	Two tests were cleared by FDA in 1984 that no longer appear to be available commercially
Soil-transmitted helminths	None
Yaws	None. There are a large number of FDA-cleared assays for syphilis that can also detect Yaws.

Vaccines

With the exception of the BCG (bacille Calmette-Guerin) vaccine, which is licensed for preventing TB, no US-approved vaccines exist for preventing diseases on the current list of NTDs. There are, however, several investigational vaccines in development to protect against malaria, TB, and dengue.