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# **Guidance for Industry Neglected Tropical Diseases of the Developing World: Developing Drugs for Treatment or Prevention**

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)**

**July 2014  
Clinical/Antimicrobial**

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# **Guidance for Industry Neglected Tropical Diseases of the Developing World: Developing Drugs for Treatment or Prevention**

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# **Guidance for Industry<sup>1</sup>**

## **Neglected Tropical Diseases of the Developing World: Developing Drugs for Treatment or Prevention**

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

### **I. INTRODUCTION**

The purpose of this guidance is to assist sponsors in the development of drugs for the treatment or prevention of neglected tropical diseases (NTDs) of the developing world.<sup>2</sup> Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall drug development program for the treatment or prevention of NTDs, as defined in section 524(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), including clinical trial designs and internal review standards to support approval of drugs.

This guidance is issued in response to section 740 of the Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act, 2010 (2010 Appropriations Act) (Public Law 111-80), dated October 21, 2009, that directed the FDA to issue guidance based on the recommendations of the NTD review group<sup>3</sup> regarding drugs being developed for the treatment or prevention of NTDs.<sup>4</sup> Section 740(b) of the 2010 Appropriations Act defines NTDs as the "tropical disease[s]" described in section 524(a)(3) of the FD&C Act. A list of the NTDs is provided in section 524(a)(3) of the FD&C Act.

This guidance is directed to sponsors who lack general knowledge about drug development issues. Pharmaceutical sponsors with experience in drug development will find this guidance to

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<sup>1</sup> This guidance has been prepared by the Office of Antimicrobial Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

<sup>2</sup> For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

<sup>3</sup> See section 740(b) of the 2010 Appropriations Act.

<sup>4</sup> Public Law 111-80 can be accessed on the United States Government Printing Office Web site at <http://www.gpo.gov/fdsys/pkg/PLAW-111publ80/pdf/PLAW-111publ80.pdf>.

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be basic, but we acknowledge that sponsors interested in evaluating investigational drugs for NTDs may have little experience in working with the FDA on drug development issues.<sup>5</sup>

Potential sponsors should understand that: (1) we will review and comment on clinical development programs for NTDs under an investigational new drug application (IND) submission, regardless of where the clinical development will take place; (2) we can approve a drug for treatment of an NTD not endemic in the United States; (3) the regulatory pathways and internal review standards for approval of drugs for NTDs are the same as for approval of drugs for diseases endemic in the United States; and (4) we are committed to exercising our regulatory authorities to facilitate access to therapies that can help reduce morbidity and mortality associated with NTDs. Specifically, FDA regulations give the FDA considerable latitude “to exercise its scientific judgment to determine the kind and quality of data and information an applicant is required to provide . . . to meet the statutory standards [for approval]” (21 CFR 314.105(c)). FDA regulations also specifically require that we consider the severity of disease and the absence of alternative satisfactory therapy in weighing whether the benefits of therapy outweigh known and potential risks (21 CFR 312.84(a)). In addition, there may be circumstances when one adequate and well-controlled trial, combined with confirmatory evidence, provides adequate evidence of efficacy.<sup>6</sup>

We also note that there is a separate draft guidance that describes the policies and procedures for the tropical disease priority review voucher described in section 524(a)(3) of the FD&C Act (21 U.S.C. 360n(a)(3)), including the procedures for adding a new disease to the list in section 524.<sup>7</sup> Section 524 allows the FDA to designate as a tropical disease any other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations.

Although this guidance focuses on drugs for the treatment of NTDs, in general many of the drug development issues for drugs used in the prevention of NTDs are similar to drug development issues for drugs used in the treatment of NTDs. Additional discussion of general clinical trial design issues and statistical analyses are addressed in the International Conference on Harmonisation (ICH) guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*.

FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should

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<sup>5</sup> The following FDA Web site has been developed to assist academic investigators and inexperienced sponsors in submitting an investigational new drug application (IND): <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm343349.htm>.

<sup>6</sup> See section 505(d) of the FD&C Act; see also section III.B., Clinical Development Considerations, of this guidance and the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

<sup>7</sup> See the draft guidance for industry *Tropical Disease Priority Review Vouchers*. When final, this guidance will represent the FDA’s current thinking on this topic.

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be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

## **II. BACKGROUND**

NTDs are infectious diseases that generally are rare or absent in developed countries, but are often widespread in the developing world. Some of the NTDs, such as tuberculosis, affect populations globally, including U.S. populations. Other NTDs, such as African trypanosomiasis, are more geographically confined. The availability of new safe and effective drugs for NTDs could provide public health benefit for overall global health, but because these diseases are found primarily in developing countries, existing incentives have been insufficient to encourage development of new drug therapies. By enacting section 524 of the FD&C Act, Congress is attempting to stimulate new drug development for NTDs by offering additional incentives for obtaining FDA approval of certain NTD drugs. Under section 524(b)(1), the sponsor of a human drug application for a tropical disease product application may be eligible for a voucher that can be used to obtain a priority review for any subsequent human drug application submitted under section 505(b)(1) of the FD&C Act or section 351 of the Public Health Service Act.

Many NTDs are transmitted by insects or contaminated food and water in parts of the world with poor sanitation and hygiene. Effective sanitation, access to clean water supplies, and other nonpharmacological interventions (e.g., use of bed nets) help to prevent initial NTD infection and help to prevent re-infection following effective treatment.

## **III. DEVELOPMENT PROGRAM**

### **A. Nonclinical Development and Chemistry, Manufacturing, and Controls Considerations**

#### *1. Pharmacology/Toxicology Studies*

Nonclinical studies provide an information base to assess whether human clinical trials of an investigational drug are reasonably safe to be conducted (21 CFR 312.23(a)(8)). The types of studies that will be needed for each drug under study for an NTD depend on the drug's intended use, the proposed clinical trial population (e.g., healthy volunteers versus patients with the infection), and proposed treatment regimen. FDA and ICH guidances addressing nonclinical studies for developing drugs are listed in Appendix 1.

Depending on the drug that will be studied under an IND, different approaches can be used to provide nonclinical information in support of the proposed use in clinical evaluations under an IND. Some of the possible approaches for nonclinical studies for NTD investigational drugs are included in the following list.

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- **Nonclinical studies of an FDA-approved drug that was approved for another indication:** Depending upon how the drug is proposed to be studied under an IND (e.g., dose, duration, route of administration, population of use), additional nonclinical studies may not be necessary and reference to the approved product labeling may be adequate. Where the manner in which the drug will be studied under an IND is different from its FDA-approved use, the information from existing studies should be reviewed in the context of the proposed indication for an NTD. Obtaining a right of reference to the actual nonclinical studies in the new drug application (NDA) or the IND may be necessary. In some cases (e.g., new route of administration for use in an NTD or a longer duration of treatment), new nonclinical studies may be needed to support a new IND submission.
- **Nonclinical studies for an investigational drug under an IND for another indication (i.e., a drug that is not an FDA-approved drug but some human data are available):** If the sponsor that holds the IND for the drug under development also wants to develop the drug for an NTD, cross-referencing existing information for the investigational drug that is being developed for another indication may be a means to provide adequate nonclinical information to support IND development for an NTD. A sponsor intending to study an indication for an NTD with a drug that is being developed by another sponsor would need to obtain a letter (i.e., right of reference) authorizing the sponsor to rely on the nonclinical portions of the original sponsor's IND for the same drug. The review division will evaluate the nonclinical studies in the context of the proposed indication for the NTD and the clinical dosing regimen to assess their adequacy to support the proposed IND development for the NTD and determine whether additional nonclinical studies may be needed.
- **Nonclinical studies of a new investigational drug:** When nonclinical studies have not been done (or referencing existing data from nonclinical studies is otherwise not an option), nonclinical studies should be conducted to collect data. In general, studies in animals should evaluate:
  - Pharmacology of the drug and its disposition (i.e., mechanism of action, absorption, distribution, metabolism, and excretion)
  - Toxicological effects of the drug
    - Acute administration (including safety pharmacology)
    - Subacute administration
    - Chronic administration (when appropriate)
  - Reproductive toxicology
  - Genetic toxicity (not needed for biological products)
  - Carcinogenicity potential, for chronically administered drugs (for biological products, the sponsor should discuss with the review division)

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As noted previously, the extent and amount of pharmacology and toxicology information needed to initiate a clinical development program under a new IND depends on the indication, proposed treatment regimen, and patient population for whom the drug is intended for use. For example, if the total duration of therapy is anticipated to be less than 6 months, animal studies to assess toxicity following *chronic* administration may not be needed. In most cases, the safety and efficacy of a new drug can be assessed in trials enrolling men and nonpregnant women; therefore, the submission of reproductive toxicology studies may not be needed for initial clinical development. However, if a drug is targeted for development in pregnant women, a full battery of reproductive toxicology studies should be completed, along with some preliminary evidence of safety and efficacy, before clinical trials in pregnant women can begin (21 CFR 312.23(a)(8)(ii)). In general, reproductive toxicology studies should be completed at the time of NDA submission.

### *2. Microbiology Considerations and Animal Models of Infection*

Nonclinical microbiology studies provide information about a drug's mechanism of action and its antimicrobial activity that help to inform drug development decisions and the design of human clinical trials. The results from antimicrobial activity studies in animal models of infection may be important to select candidate drugs to enter into clinical development and to select dosing regimens for clinical trials. Because animal models of infection do not always predict responses in humans, and animal models of infection are not available for certain NTDs, results from such studies are not required to initiate an IND and to proceed with human clinical trials. However, developing new animal models or refining existing animal models may assist overall drug development in NTDs. See the draft guidance for industry *Microbiological Data for Systemic Antibacterial Drug Products — Development, Analysis, and Presentation* for information on development, analysis, and presentation of microbiology data for IND and NDA or biologics license application (BLA) submissions for systemic antibacterial drugs.<sup>8</sup>

### *3. Chemistry, Manufacturing, and Controls*

During the review of an NDA or BLA, we assess the quality of the drug manufacturing process and establish quality standards to ensure the safety and efficacy of the drug. This evaluation includes inspection of manufacturing facilities within and outside the United States for an NDA or BLA for NTDs.

Sufficient chemistry, manufacturing, and controls (CMC) information for the new investigational drug and a placebo (if used in the trial) should be provided in an IND submission to allow evaluation of drug quality and patient safety in a proposed clinical trial. A letter of authorization to an FDA drug master file<sup>9</sup> can also be used to allow the FDA to refer to CMC information in

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<sup>8</sup> When final, this guidance will represent the FDA's current thinking on this topic.

<sup>9</sup> A drug master file (DMF) is a submission to the FDA that can be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. The information contained in the DMF can be used to support an IND; a DMF is not a substitute for an IND. For more information about DMFs, see the Guideline for Drug Master Files at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122886.htm>.



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support of an IND or NDA/BLA. See Appendix 1 for guidances relevant to IND-phase development<sup>10</sup> and when planning for the NDA.<sup>11</sup>

If a proposed investigational drug is an unmodified form of a marketed, FDA-approved drug, the established and trade names of the drug and the manufacturer's name may be sufficient to support a new IND submission from a CMC perspective; a reference to the FDA-approved product label may be adequate to meet CMC requirements.

For drugs that are already in development under another IND, a letter of authorization to that existing IND may be adequate.

For non-FDA-approved, foreign-sourced test or comparator drugs, the type of CMC information needed to ensure the quality, safety, and efficacy of drugs used in clinical trials can be discussed with the FDA before the submission of an IND (see section III.D., Other Activities in the Center for Drug Evaluation and Research).

### *4. Resources for Nonclinical Development Considerations*

The Biopharmaceutical Product Development Services program provided through the National Institute of Allergy and Infectious Diseases at the National Institutes of Health (NIH) offers a collection of nonclinical services to support the development of high-priority therapeutic candidates.<sup>12</sup> Access to such resources may help facilitate drug development for NTDs.

## **B. Clinical Development Considerations**

The demonstration of substantial evidence of safety and effectiveness of new drugs is required for approval for the treatment or prevention of disease.<sup>13</sup> Generally, this evidence is derived from two adequate and well-controlled phase 3 trials. However, we may consider “data from one adequate and well-controlled clinical investigation and confirmatory evidence” to constitute substantial evidence if we determine that such data and evidence are sufficient to establish effectiveness (section 505(d) of the FD&C Act). For example, a drug already approved for another indication may need only one adequate and well-controlled trial for approval for treatment of an NTD.<sup>14</sup>

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<sup>10</sup> See the guidances for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products* and *INDs for Phase 2 and Phase 3 Studies — Chemistry, Manufacturing, and Controls Information*.

<sup>11</sup> See the ICH guidance for industry *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*.

<sup>12</sup> Information on the Biopharmaceutical Product Development Services program at NIH can be found at <http://www.niaid.nih.gov/labsandresources/resources/dmid/pretheraagents/biopharma/Pages/default.aspx>.

<sup>13</sup> See section 505 of the FD&C Act.

<sup>14</sup> For more information, see the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

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Given the geographic distribution of most NTDs, we expect that most of the supporting safety and efficacy data for drug development programs for NTDs will be generated from outside the United States. FDA regulations permit the acceptance of foreign clinical studies in support of an NDA or BLA approval. Under 21 CFR 312.120, if certain conditions are met (including that the trial was conducted in accordance with good clinical practice, which necessitates review and approval by an independent ethics committee), we will accept as support for an application for marketing approval a well-designed and well-conducted foreign clinical trial not conducted under an IND. However, we strongly encourage sponsors who intend to seek FDA approval for a drug for NTDs to submit an IND, regardless of where the clinical development occurs, to provide an opportunity for the FDA to offer advice on the development program to ensure that it will be able to support a future NDA or BLA. Marketing approval of a new drug based solely on foreign clinical data is governed by 21 CFR 314.106.

Phase 1 and phase 2 trials play an important role in characterizing the pharmacokinetics, preliminary safety, and early evidence of activity of a drug for the treatment of an NTD. In addition to pharmacokinetic characterization, the clinical pharmacology component of the drug development program for an NTD should also employ evaluation of relevant drug interactions, effects of renal and/or hepatic impairment on the pharmacokinetics of the drug, and potential exposure-response relationships for both safety and efficacy outcomes. We can provide advice and feedback on recommendations for trial designs when submitted as part of an IND. The information from these studies in early clinical development can help to arrive at optimal dose selection(s) for phase 3 trials. Another advantage of submitting an IND is the advice from the FDA on whether the optimal dose selection for the phase 3 trial is applicable and relevant for a dose and dosing regimen for the U.S. population.<sup>15</sup>

The types of clinical trial designs for demonstration of efficacy of drugs for treatment of NTDs of the developing world are listed below (see 21 CFR 314.126(b)(2)(i) – (v)):

- **Placebo concurrent control.** The test drug is compared with an inactive preparation designed to resemble the test drug as much as possible. A placebo-controlled trial may include additional treatment groups, such as an active treatment control or a dose-comparison control, and usually includes randomization and blinding of patients or investigators, or both. Placebo-controlled trials are appropriate in situations where there is no approved treatment for an NTD, or where the administration of placebo would not raise ethical concerns.
- **Dose-comparison concurrent control.** At least two doses of the drug for which there is clinical equipoise (e.g., early phase clinical evaluations demonstrate potential clinical activity of two or more different doses) are evaluated in a clinical trial that then shows superiority of one dose over the other dose(s). A dose-comparison trial may include additional treatment groups, such as placebo control or active control. Dose-comparison trials usually include randomization and blinding of patients or investigators, or both.

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<sup>15</sup> To rely solely on foreign clinical data for marketing approval, 21 CFR 314.106(b) requires, among other things, that the data be applicable to the U.S. population and U.S. medical practice. Section 314.106(b) further provides that “FDA will apply this policy in a flexible manner according to the nature of the drug and the data being considered.”

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- **No treatment concurrent control.** Where objective measurements of effectiveness are available and placebo effect is negligible, the test drug is compared with no treatment. No treatment concurrent control trials usually include randomization.
- **Active treatment concurrent control.** The test drug is compared with known effective therapy, for example, when the condition treated is such that administration of placebo or no treatment would be contrary to the interest of the patient. An active treatment trial may include additional treatment groups, however, such as a dose-comparison control. Active treatment trials usually include randomization and blinding of patients or investigators, or both. Active treatment concurrent control can be designed to show superiority of a test drug over an active control drug, or to show noninferiority. Noninferiority of the test drug and active control drug can mean that both drugs were effective or that neither was effective. Therefore, if the intent of the trial is to show noninferiority of the test and control drugs, the active control drug should have a well-characterized and reliable treatment effect over placebo.
- **Historical control.** The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (e.g., certain malignancies) and studies in which the effect of the drug is self-evident (e.g., general anesthetics).

In general, phase 3 trials should be prospective, randomized to treatment assignment, and have treatment groups and investigators blinded to the treatment assignment (*double-blinded*), unless the trial design is a historical control. If there is a compelling reason that trials cannot be double-blinded, sponsors should discuss with the FDA the efforts to minimize potential biases of single-blind or open-label trial designs. The number of patients needed for enrollment into clinical trials depends on the type of clinical trial design, endpoints, and safety profile. The results of superiority trials usually are straightforward to interpret, when superiority trials are feasible. For the noninferiority trial designs, the noninferiority margin should be justified, ideally, at the point of protocol development for a clinical trial.

Adaptive clinical trial designs may be appropriate to consider for clinical trials of some NTDs. Clinical trials can be designed with adaptive features that may enhance the efficiency of the trial. For example, the adaptive design might result in a shorter overall duration of the trial, a fewer number of patients enrolled, or a greater likelihood of showing an effect of the drug if one exists. Sponsors who are considering an adaptive design are encouraged to consult the draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics* for review of statistical, clinical, and regulatory aspects of this potential approach.<sup>16</sup> We also encourage sponsors to

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<sup>16</sup> When final, this guidance will represent the FDA's current thinking on this topic.

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discuss such clinical trial designs with the FDA before conduct of the trial to provide an opportunity for advice on trials with an adaptation.

The size of the preapproval safety database depends on different factors, including the risks and benefits of therapy and the conditions under study, and should be discussed with the FDA during drug development. The nonclinical safety studies and reported adverse events in early clinical development should also be considered. The infectious disease's pathogenic characteristic is another factor used to determine the size of the preapproval safety database. For example, a smaller safety database might enable an appropriate ascertainment of risk-benefit for infectious diseases where the therapy prevents a serious or fatal outcome, compared to larger preapproval safety databases for infectious diseases where therapy is intended to provide symptom improvement of a less serious condition. For a drug's use in the prevention of an NTD, a larger preapproval safety database may be needed because the drug may be given to healthy people who might be exposed to the infectious agent.

Human efficacy studies are ethical and feasible for most NTDs. Therefore, the rule "Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible" (21 CFR 314.600 for NDAs; 21 CFR 601.90 for BLAs) may not be an appropriate regulatory pathway for a new drug approval for NTDs.

We encourage sponsors who are planning clinical trials to discuss their planned trials with the FDA and to get feedback on their proposed trial designs. We have available on the FDA Web site a number of guidances that provide valuable information on the design and conduct of clinical trials for studying new therapies. A list of guidances pertinent to the clinical evaluation of drugs for NTDs is included in Appendix 2.

### **C. Regulatory Considerations**

There are regulatory paradigms or tools that can be used in the area of drug development for NTDs when appropriate. Additional information for sponsors regarding each of these procedures can be found on the FDA Web site, referenced below in the appropriate sections.

- **Orphan Product Designation.** The Office of Orphan Product Development (OOPD) serves a mission to promote the development of drugs for treatment of rare diseases and conditions. Most of the NTDs would be considered orphan diseases among the U.S. population. Thus, a drug being developed for an NTD may be considered for designation as an orphan product, which has certain benefits for a sponsor. OOPD supports product development for rare diseases through an extramural grants program. A sponsor can submit an application to the OOPD for consideration for orphan designation.<sup>17</sup>
- **Expedited Programs for Serious Conditions.** The following programs are intended to facilitate and expedite development and review of new drugs to address unmet medical needs in the treatment of serious or life-threatening conditions:

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<sup>17</sup> Information about orphan designation can be found on the FDA Web site at <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/default.htm>.

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- Fast track designation
- Breakthrough therapy designation
- Accelerated approval
- Priority review designation

Sponsors should consult the draft guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics* to determine whether any of these programs may be applicable to their development programs.<sup>18</sup> That guidance describes the qualifying criteria and features (e.g., benefits) of each of the expedited programs.

- **Tropical Disease Priority Review Voucher.** The Tropical Disease Priority Review program provides for a voucher that is awarded at the time of approval of certain drugs that prevent or treat a tropical disease (i.e., NTD) that subsequently can be redeemed for a priority review of an application for a drug for any indication submitted at a later time.<sup>19</sup>
- **Qualified Infectious Disease Product.** An antibacterial or antifungal drug intended for the treatment of serious or life-threatening NTD infections may qualify for designation as a qualified infectious disease product (see section 505E(g) of the FD&C Act). A designation as a qualified infectious disease product has certain regulatory incentives, including an extension of the drug's exclusivity period.

### **D. Other Activities in the Center for Drug Evaluation and Research**

The following activities in the Center for Drug Evaluation and Research (CDER) pertain to developing drugs for NTDs.

- **Pre-IND Consultation Program.** Sponsors interested in developing a drug for NTDs in developing countries should contact the FDA and discuss their nonclinical and clinical development plans with the appropriate review division within the Office of Antimicrobial Products. Our pre-IND program allows sponsors to receive direct feedback on their proposed content of an IND submission, including the types of nonclinical studies that should accompany the IND, and anticipated clinical trial designs. Sponsors have an opportunity to consider our recommendations when planning their studies.<sup>20</sup>

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<sup>18</sup> When final, this guidance will represent the FDA's current thinking on this topic.

<sup>19</sup> See the draft guidance for industry *Tropical Disease Priority Review Vouchers*.

<sup>20</sup> The Office of Antimicrobial Products maintains a Pre-IND Consultation Program Web site at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/default.htm>.

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- **CDER Review Processes.** The internal review processes for INDs and NDAs or BLAs are described on the FDA Web site. Timelines are provided for FDA application review as well as types of communications between sponsors and the FDA.<sup>21</sup>

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<sup>21</sup> An overview of the FDA review of drug development and approval can be found at the following Web sites:  
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm#FDA%20Guidances%20for%20Investigational%20New%20Drugs> and  
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm>.

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### **APPENDIX 1: GUIDANCES FOR NONCLINICAL DEVELOPMENT AND CHEMISTRY, MANUFACTURING, AND CONTROLS<sup>22</sup>**

The following guidances provide relevant information on nonclinical development for sponsors interested in developing a drug for an NTD. Sponsors should follow the recommendations in these guidances when submitting an IND to begin clinical investigations.

- The ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* provides an overall description of what nonclinical studies generally are needed at any stage of drug development and when they are needed. For biological products, ICH M3(R2) provides guidance on the timing of nonclinical studies relative to clinical development.
- The ICH guidance for industry *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* provides guidance for manufacturing under an appropriate system for managing quality.
- The ICH guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* provides an overall description of what nonclinical studies of biological products should be considered to support clinical trials.
- The draft guidance for industry *Microbiological Data for Systemic Antibacterial Drug Products — Development, Analysis, and Presentation* provides an overview of the nonclinical microbiology studies that help to support clinical development.<sup>23</sup>
- The guidance for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products* describes in general the types of information that should accompany an IND submission. See also the Questions and Answers companion document.
- The guidance for industry *INDs for Phase 2 and Phase 3 Studies — Chemistry, Manufacturing, and Controls Information* describes the CMC information that should be submitted for phase 2 and phase 3 trials conducted under INDs.

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<sup>22</sup> These guidances can be found on the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

<sup>23</sup> When final, this guidance will represent the FDA's current thinking on this topic.

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### **APPENDIX 2: GUIDANCES FOR CLINICAL DEVELOPMENT<sup>24</sup>**

The following guidances can be useful in the area of clinical development of drugs for NTDs:

- The ICH guidance for industry *E9 Statistical Principles for Clinical Trials* summarizes statistical areas for clinical trials.
- The ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials* highlights some of the important aspects of using an appropriate control group. The guidance discusses some of the considerations for the noninferiority trial to ensure the appropriate demonstration of efficacy when compared to an active-controlled drug.
- Effective treatment of some NTDs includes the use of combinations of antimicrobial drugs to enhance efficacy or prevent the development of resistant pathogens. Some development programs may include two or more new investigational drugs. The guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination* covers this area.
- Some NTDs have known effective treatment, and clinical trials designed to demonstrate noninferiority of an investigational drug to the control drug can be used in this situation. The noninferiority clinical trial design poses some unique scientific and regulatory challenges, which focus on an ability to describe a reliable treatment effect of the control drug. Two guidances in this area include the draft guidance for industry *Non-Inferiority Clinical Trials*<sup>25</sup> and the guidance for industry *Antibacterial Drug Products: Use of Noninferiority Trials to Support Approval*.
- The principles of good meeting management practices and standardized procedures for meetings are outlined in the guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants*.
- The guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* provides a general overview of the approach to demonstrating effectiveness.
- The draft guidance for industry *Antibacterial Therapies for Patients With Unmet Medical Need for the Treatment of Serious Bacterial Diseases* explains the FDA's current thinking about possible streamlined development programs and clinical trial designs for drugs to treat serious bacterial diseases in patients who have an unmet medical need.<sup>26</sup>

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<sup>24</sup> These guidances can be found on the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

<sup>25</sup> When final, this guidance will represent the FDA's current thinking on this topic.

<sup>26</sup> When final, this guidance will represent the FDA's current thinking on this topic.



### *Contains Nonbinding Recommendations*

- The draft guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics* is a single resource for information on the FDA’s policies and procedures for fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation.<sup>27</sup>

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<sup>27</sup> When final, this guidance will represent the FDA’s current thinking on this topic.