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

DRAFT GUIDANCE

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

**August 2011
Clinical/Antimicrobial**

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

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1 **Guidance for Industry¹**
2 **Neglected Tropical Diseases of the Developing World:**
3 **Developing Drugs for Treatment or Prevention**
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8 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current
9 thinking on this topic. It does not create or confer any rights for or on any person and does not operate to
10 bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of
11 the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA
12 staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call
13 the appropriate number listed on the title page of this guidance.
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18 **I. INTRODUCTION**
19

20 The purpose of this guidance is to assist sponsors in the clinical development of drugs for the
21 treatment or prevention of neglected diseases of the developing world.² Specifically, this
22 guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the
23 overall drug development program for the treatment or prevention of neglected tropical diseases
24 (NTDs), as defined in section 524(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C
25 Act), including clinical trial designs and internal review standards to support approval of drugs.
26 This draft guidance is intended to serve as a focus for continued discussions among the review
27 divisions in the Office of Antimicrobial Products, pharmaceutical sponsors, the academic
28 community, and the public.
29

30 This guidance addresses section 740 of the Agriculture, Rural Development, Food and Drug
31 Administration and Related Agencies Appropriations Act, 2010 (Public Law 111-80), dated
32 October 21, 2009, that directed the FDA to provide guidance in the form of general
33 recommendations and regulatory considerations for drugs being developed for the treatment or
34 prevention of NTDs.³ Section 740 references the NTDs included in section 524(a)(3) of the
35 FD&C Act, as follows:
36

¹ 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.

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

³ 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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- 37 • Tuberculosis
- 38 • Malaria
- 39 • Blinding trachoma
- 40 • Buruli Ulcer
- 41 • Cholera
- 42 • Dengue/dengue hemorrhagic fever
- 43 • Dracunculiasis (guinea-worm disease)
- 44 • Fascioliasis
- 45 • Human African trypanosomiasis
- 46 • Leishmaniasis
- 47 • Leprosy
- 48 • Lymphatic filariasis
- 49 • Onchocerciasis
- 50 • Schistosomiasis
- 51 • Soil-transmitted helminths
- 52 • Yaws

53
54 This guidance is intended to clarify the regulatory requirements for drug approval in the United
55 States as well as the internal review standards for drugs for these NTDs. Specifically, this
56 guidance is directed to sponsors who lack general knowledge about drug development issues.
57 Pharmaceutical sponsors with experience in drug development will find this guidance to be
58 basic, but we acknowledge that sponsors interested in evaluating investigational drugs for NTDs
59 may have little experience in working with the FDA on drug development issues, and this
60 guidance is intended to help them better understand the FDA processes.

61
62 Potential sponsors should understand that: (1) we will review and comment on clinical
63 development programs for NTDs under an investigational new drug application (IND)
64 submission, regardless of where the clinical development will take place; (2) we can approve a
65 drug for treatment of an NTD not endemic in the United States; (3) the regulatory pathways and
66 internal review standards for approval of drugs for NTDs are the same as for approval of drugs
67 for diseases endemic in the United States; and (4) we are committed to exercising our regulatory
68 authorities to facilitate access to therapies that can help reduce morbidity and mortality
69 associated with NTDs. Specifically, FDA regulations give the FDA considerable latitude “to
70 exercise its scientific judgment to determine the kind and quality of data and information an
71 applicant is required to provide . . . to meet the statutory standards [for approval]” (21 CFR
72 314.105(c)). FDA regulations also specifically require that we consider the severity of disease
73 and the absence of alternative satisfactory therapy in weighing whether the benefits of therapy
74 outweigh known and potential risks (21 CFR 312.84(a)). In addition, there may be
75 circumstances when one trial provides adequate evidence of efficacy.⁴

76

⁴ See 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>. See also section III.B., Clinical Development Considerations, in this guidance.

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77 We also note that there is a separate guidance that describes the policies and procedures for the
78 tropical disease priority review voucher described in section 524(a)(3) of the FD&C Act (21
79 U.S.C. 360n(a)(3)), including the procedures for adding a new disease to the list in section 524.⁵
80 Section 524 allows the FDA to designate as an NTD any other infectious disease for which there
81 is no significant market in developed nations and that disproportionately affects poor and
82 marginalized populations.

83
84 Although this guidance focuses on drugs for the treatment of NTDs, in general many of the drug
85 development issues for drugs used in the prevention of NTDs are similar to drug development
86 issues for drugs used in the treatment of NTDs. Additional discussion of general clinical trial
87 design issues and statistical analyses are addressed in the International Conference on
88 Harmonisation (ICH) guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10*
89 *Choice of Control Group and Related Issues in Clinical Trials*.

90
91 FDA's guidance documents, including this guidance, do not establish legally enforceable
92 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
93 be viewed only as recommendations, unless specific regulatory or statutory requirements are
94 cited. The use of the word *should* in Agency guidances means that something is suggested or
95 recommended, but not required.

96
97

98 **II. BACKGROUND**

99

100 NTDs are infectious diseases that generally are rare or absent in developed countries, but are
101 often widespread in the developing world. Some of the NTDs, such as tuberculosis, affect
102 populations globally, including U.S. populations. Other NTDs, such as African trypanosomiasis,
103 are more geographically confined but have high case-fatality rates. Most of the NTDs have at
104 least one drug that is FDA-approved for treatment of the particular NTD, but a few of the NTDs
105 do not have FDA-approved drugs for treatment. The availability of new safe and effective drugs
106 for NTDs could provide public health benefit for overall global health, but because these
107 diseases are found primarily in poor and developing countries, existing incentives have been
108 insufficient to encourage development of new and innovative drug therapies. By enacting
109 section 524, Congress is attempting to stimulate new drug development by offering additional
110 incentives for obtaining FDA approval of certain NTD drugs.

111

112 Many NTDs are transmitted by insects or contaminated food and water in parts of the world with
113 poor sanitation and hygiene. Effective sanitation, access to clean water supplies, and other
114 nonpharmacological interventions (e.g., use of bed nets) help to prevent initial NTD infection
115 and help to prevent re-infection following effective treatment. We encourage
116 nonpharmacological interventions to be employed concurrent with drug development.

117

118

⁵ 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. For the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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119 III. DEVELOPMENT PROGRAM

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121 A. Nonclinical Development Considerations

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123 I. Pharmacology/Toxicology Studies

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125 Nonclinical studies provide an information base to assess whether human clinical trials of an
126 investigational drug are reasonably safe to be conducted (21 CFR 312.23(a)(8)). The types of
127 studies that will be needed for each drug under study for an NTD depends on its intended use,
128 the proposed clinical trial population (e.g., healthy volunteers versus patients with the infection;
129 adults versus children), and proposed treatment regimen. Guidances addressing nonclinical
130 studies for developing drugs are already available from the FDA and ICH, and the relevant
131 guidances to assist sponsors in development of drugs for NTDs are listed in Appendix 1.

132

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

137

138 • **Nonclinical studies of an FDA-approved drug that was approved for another**
139 **indication:** Depending upon how the drug is proposed to be studied under IND (e.g.,
140 dose, duration, route of administration, population of use), reference to the approved
141 product labeling may be adequate. In the setting where the manner in which the drug will
142 be studied under IND is different from its FDA-approved use, the information from
143 existing studies should be reviewed. Obtaining a right of reference to the actual
144 nonclinical studies in the new drug application (NDA) or the IND may be necessary. The
145 review division will evaluate the original nonclinical studies in the context of the
146 proposed indication for an NTD. In certain situations in which the proposed use of the
147 drug for an NTD is different than its labeled use (e.g., new route of administration for use
148 in an NTD or a longer duration of treatment), new nonclinical studies may be needed to
149 support a new IND submission.

150

151 • **Nonclinical studies for an investigational drug under clinical development under**
152 **IND for another indication (i.e., a drug that is not an FDA-approved drug but some**
153 **human data are available):** If the same sponsor that holds the IND for the drug under
154 development also wants to develop the drug for a neglected disease, cross-referencing
155 existing information for the investigational drug that is being developed for another
156 indication may be a means to provide adequate nonclinical information to support IND
157 development for an NTD. The sponsor can cross-reference its own existing nonclinical
158 studies in the IND. A sponsor intending to study an indication for a neglected disease
159 with a drug that is being developed by another sponsor would need to obtain a letter (i.e.,
160 right of reference) authorizing the sponsor to rely on the nonclinical portions of the
161 original sponsor's IND for the same drug. The review division will evaluate the
162 nonclinical studies in the context of the proposed indication for an NTD and clinical
163 dosing regimen to assess their adequacy to support the proposed IND development for an
164 NTD and determine whether additional nonclinical studies may be needed.

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- **Nonclinical studies of a new investigational drug:** When nonclinical studies have not been done (e.g., referencing existing data from nonclinical studies is not an option), they should be conducted to collect data. In general, studies in animals should evaluate the following characteristics of a new drug:
 - Pharmacology of the drug and its disposition (i.e., absorption, distribution, metabolism, and excretion)
 - Toxicological effects of the drug
 - Acute administration (including safety pharmacology)
 - Subacute administration
 - Chronic administration (when appropriate)
 - Reproductive toxicology studies
 - 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 intended patient population. 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 are required, along with some preliminary safety and evidence of activity, 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.

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2. Microbiology Considerations and Animal Models of Infection

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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. The list in Appendix 1 includes a draft guidance for industry

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210 on development, analysis, and presentation of microbiology data for IND and NDA or biologics
211 license application (BLA) submissions.⁶

212

213 3. *Chemistry, Manufacturing, and Controls*

214

215 We assess the quality of the drug manufacturing process and establish quality standards to ensure
216 the safety and efficacy of new drugs. During the review of an NDA or BLA, we evaluate drug
217 manufacturing quality standards for the drug. This evaluation includes inspection of
218 manufacturing facilities outside the United States for an NDA or BLA for NTDs.

219

220 Sufficient chemistry, manufacturing, and controls (CMC) information for the new investigational
221 drug and a placebo (if used in the trial) should be provided in an IND submission to allow
222 evaluation of drug quality and patient safety in a proposed clinical trial. A letter of authorization
223 to an FDA drug master file⁷ can also be used to allow the FDA to refer to CMC information in
224 support of an IND or NDA/BLA. See Appendix 1 for guidances relevant to IND-phase
225 development⁸ and when planning for the NDA.⁹

226

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

231

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

234

235 For non-FDA-approved, foreign-sourced test or comparator drugs, a pre-IND approach is
236 recommended to discuss what type of CMC information would be needed to ensure the quality,
237 safety, and efficacy of drugs used in clinical trials.

238

⁶ See the draft guidance for industry *Microbiological Data for Systemic Antibacterial Drug Products — Development, Analysis, and Presentation*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁷ 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>.

⁸ 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*.

⁹ See the ICH guidance for industry *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*.

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239 4. *Other Nonclinical Considerations*

240
241 Financial and laboratory resources for nonclinical studies may not be readily available for
242 developers of drugs to treat NTDs. A government resource that can be useful to developers is
243 the Product Development Services provided through the National Institute of Allergy and
244 Infectious Diseases (NIAID) at the National Institutes of Health (NIH). NIAID offers a
245 collection of nonclinical services to support the development of high-priority therapeutic
246 candidates.¹⁰ Access to such resources may help facilitate drug development for NTDs.

247 248 **B. Clinical Development Considerations**

249
250 The demonstration of substantial evidence of effectiveness of new drugs is required for approval
251 for the treatment or prevention of disease.¹¹ Generally, this evidence can be derived from two
252 adequate and well-controlled phase 3 trials. However, we may consider “data from one adequate
253 and well-controlled clinical investigation and confirmatory evidence” to constitute substantial
254 evidence if we determine that such data and evidence are sufficient to establish effectiveness
255 (section 115(a) of the Food and Drug Administration Modernization Act of 1997 (FDAMA)
256 amended section 505(d) of the FD&C Act). For example, a drug already approved for another
257 indication may need only one adequate and well-controlled trial for approval for treatment of an
258 NTD.¹² Given the geographic distribution of most NTDs, we expect that the clinical trials
259 conducted to demonstrate safety and efficacy will be conducted outside of the United States.
260 Sponsors who ultimately seek FDA approval for a drug for NTDs should submit an IND,
261 regardless of where the clinical development occurs. In this situation, we have an opportunity to
262 provide advice and feedback to the sponsor on its entire drug development program.

263
264 Phase 1 and phase 2 studies play an important role in characterizing the pharmacokinetics,
265 preliminary safety, and early evidence of activity of a drug for the treatment of an NTD. We can
266 provide advice and feedback on recommendations for trial designs when submitted as part of an
267 IND. The information from these studies in early clinical development can help to arrive at
268 optimal dose selection(s) for phase 3 trials.

269
270 The types of clinical trial designs for demonstration of efficacy of drugs for treatment of NTDs
271 of the developing world are listed below, as derived from 21 CFR 314.126(b)(2)(i) – (v):

- 272
273 • **Placebo concurrent control.** The test drug is compared with an inactive preparation
274 designed to resemble the test drug as much as possible. A placebo-controlled trial may
275 include additional treatment groups, such as an active treatment control or a dose-
276 comparison control, and usually includes randomization and blinding of patients or
277 investigators, or both. Placebo-controlled trials are appropriate in situations where there

¹⁰ Information on the Product Development Services at NIH can be found at
<http://www.niaid.nih.gov/LabsAndResources/resources/dmid/Pages/therapeutics.aspx>.

¹¹ See section 505 of the FD&C Act.

¹² For more information, see the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

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278 is no approved treatment for an NTD, or where the administration of placebo would not
279 have ethical concerns.

280

281 • **Dose-comparison concurrent control.** At least two doses of the drug for which there is
282 clinical equipoise are evaluated in a clinical trial. A dose-comparison trial may include
283 additional treatment groups, such as placebo control or active control. Dose-comparison
284 trials usually include randomization and blinding of patients or investigators, or both.

285

286 • **No treatment concurrent control.** Where objective measurements of effectiveness are
287 available and placebo effect is negligible, the test drug is compared with no treatment.
288 No treatment concurrent control trials usually include randomization.

289

290 • **Active treatment concurrent control.** The test drug is compared with known effective
291 therapy, for example, when the condition treated is such that administration of placebo or
292 no treatment would be contrary to the interest of the patient. An active treatment trial
293 may include additional treatment groups, however, such as a dose-comparison control.
294 Active treatment trials usually include randomization and blinding of patients or
295 investigators, or both. Active treatment concurrent control can be designed to show
296 superiority of a test drug over an active control drug, or to show noninferiority.
297 Noninferiority of the test drug and active control drug can mean that both drugs were
298 effective or that neither was effective. Therefore, if the intent of the trial is to show
299 noninferiority of the test and control drugs, the active control drug should have a well-
300 characterized and reliable treatment effect over placebo.

301

302 • **Historical control.** The results of treatment with the test drug are compared with
303 experience historically derived from the adequately documented natural history of the
304 disease or condition, or from the results of active treatment, in comparable patients or
305 populations. Because historical control populations usually cannot be as well assessed
306 with respect to pertinent variables as can concurrent control populations, historical
307 control designs are usually reserved for special circumstances. Examples include studies
308 of diseases with high and predictable mortality (e.g., certain malignancies) and studies in
309 which the effect of the drug is self-evident (e.g., general anesthetics).

310

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

320

321 Adaptive clinical trial designs may be appropriate to consider for clinical trials of some NTDs.
322 Clinical trials can be designed with adaptive features that may enhance the efficiency of the trial.
323 For example, the adaptive design might result in a shorter overall duration of the trial, a fewer

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324 number of patients enrolled, or a greater likelihood of showing an effect of the drug if one exists.
325 Sponsors who are considering an adaptive design are encouraged to consult the draft guidance
326 for industry *Adaptive Design Clinical Trials for Drugs and Biologics* for review of statistical,
327 clinical, and regulatory aspects of this potential approach.¹³ We also encourage sponsors to
328 discuss such clinical trial designs with the FDA before conduct of the trial to provide an
329 opportunity for advice on trials with an adaptation.

330
331 Most of the supporting safety and efficacy data for drug development programs for NTDs will be
332 generated from outside the United States. FDA regulations permit the acceptance of foreign
333 clinical studies in support of an NDA or BLA approval. Under 21 CFR 312.120, if certain
334 conditions are met (including that the trial was conducted in accordance with good clinical
335 practice and underwent review and approval by an independent ethics committee), we will accept
336 as support for an application for marketing approval a completed well-designed and well-
337 conducted foreign clinical trial not conducted under an IND. However, we strongly encourage
338 submission of an IND so that the development program will be sufficient to support a future
339 NDA or BLA.

340
341 It is important that clinical trials be designed to include assessment of the safety of the drug
342 under study. The size of the preapproval safety database depends on different factors, including
343 the risk-benefit of therapy and the conditions under study. The nonclinical safety studies and
344 reported adverse events in early clinical development should also be considered. The infectious
345 disease's pathogenic characteristic is another factor used to determine the size of the preapproval
346 safety database. For example, a smaller safety database might enable an appropriate
347 ascertainment of risk-benefit for infectious diseases where the therapy prevents a serious or fatal
348 outcome, compared to larger preapproval safety databases for infectious diseases where therapy
349 treats symptom improvement of a less serious condition. For a drug's use in the prevention of an
350 NTD, a larger preapproval safety database may be needed because the drug may be given to
351 healthy people who might be exposed to the infectious agent.

352
353 Human efficacy studies are ethical and feasible for most NTDs. Therefore, the rule "Approval of
354 New Drugs When Human Efficacy Studies Are Not Ethical or Feasible" (21 CFR 314.600 for
355 NDAs; 21 CFR 601.90 for BLAs) may not be an appropriate regulatory pathway for a new drug
356 approval for NTDs.

357
358 We encourage sponsors who are planning clinical trials to discuss their planned trials with the
359 FDA and to get feedback on their proposed trial designs. We have available on the FDA Web
360 site a number of guidances that provide valuable information on the design and conduct of
361 clinical trials for studying new therapies. A list of guidances pertinent to the clinical evaluation
362 of drugs for NTDs is included in Appendix 2.

363

¹³ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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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.¹⁴
- **Fast Track Designation.** Drugs that are being developed for NTDs are often in a setting in which the drug is used to treat a serious disease and meet an unmet medical need.¹⁵ To facilitate development of such drugs, fast track designation was authorized as part of FDAMA. Even if there is existing therapy, a drug may still be granted fast track designation if there is evidence of advantages over existing therapy, such as superior therapeutic effects or a better safety profile. Sponsors that receive fast track designation for their drug are encouraged to meet frequently with the FDA to discuss clinical development plans. Sponsors can also submit completed sections of a BLA or NDA as part of a rolling review for the FDA to begin its efficacy and safety evaluation on a resource-available basis.
- **Priority Review Designation.** Under the Prescription Drug User Fee Act (PDUFA), goals for specific time frames to complete the review of an NDA or BLA have been established. For a drug that receives a standard review, the PDUFA goal for completing the review is 10 months. For drugs that offer safe and effective treatment of an NTD where no satisfactory alternative therapies exist or demonstrate a significant improvement compared to marketed drugs, the drug may receive a priority review designation.¹⁶ The goal for completing a priority review of a marketing application is 6 months. An NDA or BLA for treatment of an NTD that meets the criteria for a priority review would be eligible for a priority review designation.
- **Accelerated Approval.** We may base a regulatory decision on a surrogate endpoint or on a clinical endpoint other than survival or irreversible morbidity; this may considerably

¹⁴ Information about orphan designation can be found on the FDA Web site at <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/default.htm>.

¹⁵ See the “Fast Track, Accelerated Approval, and Priority Review” FDA Web site at <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccessToImportantNewTherapies/ucm128291.htm#fast>.

¹⁶ See the Manual of Policies and Procedures 6020.3R *Review Classification Policy: Priority (P) and Standard (S)* available at <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/default.htm>.

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401 shorten the time for a drug to receive FDA approval for serious or life-threatening
402 illnesses (see 21 CFR 314.510 for NDAs and 21 CFR 601.40 for BLAs).¹⁷ A surrogate
403 endpoint is a laboratory measurement or physical sign that is an indirect measurement of
404 a clinically important outcome. Under the accelerated approval regulatory paradigm, the
405 approval of the drug is granted on the condition that the clinical benefits of the drug are
406 later verified in additional clinical trials. For evaluation of certain drugs for NTDs, the
407 clinical benefits may not be evident for many years, because the effects on morbidity or
408 mortality are not evident for many years. In these circumstances, a surrogate endpoint
409 reasonably likely to predict clinical benefit can be used as the basis for accelerated
410 approval, while the verification of the clinical benefits of the drug is ongoing. For the
411 evaluation of drugs for NTDs directed at clinical responses that are readily and promptly
412 measured, there may be no need to consider surrogate endpoints because the clinical
413 response can be used for the full approval without the use of the accelerated approval
414 regulation.

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- 416 • **Tropical Disease Priority Review Voucher.** The Tropical Disease Priority Review
417 program provides for a voucher that is awarded at the time of approval of certain drugs
418 that treat a designated NTD that can subsequently be redeemed for a priority review of a
419 drug submitted at a later time, for any indication.¹⁸

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

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422 The following activities in the Center for Drug Evaluation and Research (CDER) pertain to
423 developing drugs for NTDs.
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- 426 • **Pre-IND Consultation Program.** Sponsors interested in developing a drug for NTDs in
427 developing countries should contact the FDA and discuss their nonclinical and clinical
428 development plans with the appropriate review division within the Office of
429 Antimicrobial Products. Our pre-IND program allows sponsors to receive direct
430 feedback on their proposed content of an IND submission, including the types of
431 nonclinical studies that should accompany the IND, and anticipated clinical trial designs.
432 Sponsors have an opportunity to consider our recommendations when planning their
433 studies.¹⁹
- 434

¹⁷ See also the “Fast Track, Accelerated Approval, and Priority Review” FDA Web site at <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccessToImportantNewTherapies/ucm128291.htm#fast>.

¹⁸ 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. For the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

¹⁹ The Office of Antimicrobial Products maintains a Pre-IND Consultation Web site at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/default.htm>.

Contains Nonbinding Recommendations

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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.²⁰

²⁰ 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 DEVELOPMENT²¹

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 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. See also the draft *Addendum to ICH S6: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6(R1)*.
- 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.²²
- 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.

²¹ These guidances can be found on the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

²² When final, this guidance will represent the FDA's current thinking on this topic.

APPENDIX 2: GUIDANCES FOR CLINICAL DEVELOPMENT²³

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 unmarketed investigational drugs. The draft guidance for industry *Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination* covers this area.²⁴
- 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*²⁵ 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.

²³ These guidances can be found on the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

²⁴ When final, this guidance will represent the FDA’s current thinking on this topic.

²⁵ When final, this guidance will represent the FDA’s current thinking on this topic.