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COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products

Guidance for Industry and Investigators

May 2020

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

Preface

Public Comment

This guidance is being issued to address the Coronavirus Disease 2019 (COVID-19) public health emergency. This guidance is being implemented without prior public comment because the Food and Drug Administration (FDA or Agency) has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 371(h)(1)(C)) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to <https://www.regulations.gov>. All comments should be identified with the docket number FDA-2020-D-1136 and complete title of the guidance in the request.

Additional Copies

Additional copies are available from the FDA web page titled "COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders," *available at* <https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders> and the FDA webpage titled "Search for FDA Guidance Documents," *available at* <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>. You may also send an e-mail request to COVID19-productdevelopment@fda.hhs.gov to receive an additional copy of the guidance. Please include the docket number FDA-2020-D-1136 and complete title of the guidance in the request.

Questions

For questions about this document, contact (CDER) Robert Berlin at 301-796-8828 or email robert.berlin@fda.hhs.gov or (CBER) Office of Communication, Outreach, and Development at 1-800-835-4709 or 240-402-8010 or email ocod@fda.hhs.gov.

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This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

FDA plays a critical role in protecting the United States from threats such as emerging infectious diseases, including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to providing timely guidance to support response efforts to this pandemic.

FDA is issuing this guidance to provide general considerations to assist sponsors in preparing pre-investigational new drug application (pre-IND) meeting requests for COVID-19 related drugs¹ for the duration of the COVID-19 public health emergency. As described in further detail in this guidance, FDA recommends that sponsors initiate all drug development interactions for COVID-19 related drugs through IND meeting requests.

This guidance is intended to provide sponsors with an initial framework to help organize their pre-IND meeting requests during the COVID-19 public health emergency. This document is intended to complement other guidance documents providing recommendations regarding drug

¹ For the purposes of this guidance, all references to *drugs* include both human drugs and biological products unless otherwise specified.

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development programs for COVID-19, including the guidance for industry *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention* (May 2020).²

This policy is intended to remain in effect only for the duration of the public health emergency related to COVID-19 declared by the Secretary of Health and Human Services (HHS) on January 31, 2020, effective January 27, 2020, including any renewals made by the HHS Secretary in accordance with section 319(a)(2) of the Public Health Service Act (PHS Act) (42 U.S.C. 247d(a)(2)).

Given this public health emergency, and as discussed in the Notice in the *Federal Register* of March 25, 2020, titled “Process for Making Available Guidance Documents Related to Coronavirus Disease 2019,” available at <https://www.govinfo.gov/content/pkg/FR-2020-03-25/pdf/2020-06222.pdf>, this guidance is being implemented without prior public comment because FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 371(h)(1)(C)) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency’s good guidance practices.

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

II. BACKGROUND

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named “SARS-CoV-2” and the disease it causes has been named “Coronavirus Disease 2019”. On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.³ In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.⁴

FDA is committed to supporting all scientifically sound approaches to attenuating the clinical effect of COVID-19 and to doing so in a timely and efficient manner commensurate with the urgent clinical need. Given the numerous inquiries and applications from prospective sponsors

² We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

³ Secretary of Health and Human Services Alex M. Azar, Determination that a Public Health Emergency Exists (January 31, 2020), renewed April 21, 2020, available at <https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx>.

⁴ Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak (March 13, 2020), available at <https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/>.

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interested in conducting clinical trials for COVID-19, it is essential that the Agency receive key information that will help enable us to efficiently address proposals and ensure they are properly evaluated and managed in a timely manner.

FDA is issuing this guidance to facilitate a sponsor's preparation of, and FDA's review of, a pre-IND meeting request. Well-prepared pre-IND meeting requests should enable more timely initiation of clinical trials under an IND. Note that the general principles set forth in this guidance apply to drugs; however, for cellular and gene therapies, blood products, vaccines, and other complex biological products regulated by the Center for Biologics Evaluation and Research (CBER), there may be additional considerations. FDA encourages sponsors to contact the CBER Product Jurisdiction Office at CBERProductJurisdiction@fda.hhs.gov for additional information.

III. PRE-IND PROCESS

During the current public health emergency, with the large number of potential therapeutics for COVID-19 related illness, it is essential that the review process for investigational drugs be as efficient as possible. To facilitate this, we are urging sponsors to submit a pre-IND meeting request that allows early and thorough review and discussion between the sponsor and FDA, which can lead to more rapid review of the subsequent IND and assurance of subject safety, which in turn can facilitate faster clinical trial initiation for programs that proceed to that phase. Given the range in clinical manifestations of COVID-19 and the large number of drugs and mechanisms of action being evaluated for use in this disease, the Center for Drug Evaluation and Research (CDER) has established a multispecialty, multidisciplinary team focused on review of drug development proposals.

We recommend that sponsors seek initial advice under pre-IND meeting requests.⁵ For the purposes of our response to the COVID-19 public health emergency, we are consolidating the typical pre-IND meeting request and package development process into a single step. For pre-IND requests for drugs that treat or prevent COVID-19, the content requests and processes described within this guidance substitute for those used in other settings, which FDA has described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017).⁶

The sponsor should submit a pre-IND meeting request in accordance with the process outlined in section V., Additional Resources, below. For both CDER and CBER, the sponsor should submit the meeting request with any specific questions to FDA. The pre-IND meeting request will be

⁵ For the purposes of this guidance, the pre-IND meeting request should include all relevant materials for FDA's evaluation, including the meeting package, questions, and protocol.

⁶ 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 guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

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reviewed and generally responded to as a written response only meeting.⁷ FDA's review and advice for the pre-IND meeting request will be expedited and prioritized based upon the completeness of the submission and scientific merit.⁸ Following review of the pre-IND meeting request, FDA will work with the sponsor to help ensure that all necessary information has been submitted. This pre-IND review will help result in a more efficient review of the subsequent IND submission.

For those sponsors who already have an active IND for a drug in development, or have submitted a pre-IND meeting request or IND to FDA to investigate expanding the use of their FDA-approved drug for a non-COVID-19 indication, FDA recommends submitting a new pre-IND meeting request for a proposed COVID-19 indication, rather than amending their current submissions.

Separating the COVID-19 indication for study will help FDA to quickly identify, prioritize, and assess the proposed trial to ensure that it is designed to address the current public health emergency and assure the rights and safety of subjects. The sponsor should cross-reference any other new drug application (NDA), biologics license application (BLA), or IND for the drug, but the sponsor should submit the proposal only through the new pre-IND meeting request.

IV. PRE-IND MEETING REQUEST CONTENT

A. General Considerations

Sponsors submitting pre-IND meeting requests for COVID-19 drug development should consider the following:

- Sponsors should submit pre-IND meeting requests in accordance with the process outlined in section V., Additional Resources, below. Notably, even when a sponsor has an IND open within a review division or office for another indication, the new pre-IND may not be reviewed within that same division or office.
- We recommend that all sponsors initiate COVID-19 drug development discussions under a pre-IND meeting request, instead of a pre-emergency use authorization (pre-EUA) request. Providing information in a pre-IND meeting request will generally facilitate a more efficient development process. If a drug is a good candidate for an EUA, initiating discussion under a pre-IND meeting request does not preclude submission of an EUA request to FDA in the future, if appropriate. However, at the time a sponsor initiates drug development discussions with FDA, there will generally be insufficient information to

⁷ Written response only communications from FDA are used commonly by the Agency to respond to sponsor concerns in lieu of a face-to-face or teleconference meeting.

⁸ For additional information regarding FDA efforts to prioritize review activities, see the Coronavirus Treatment Acceleration Program (CTAP) web page at <https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap>.

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assess whether, or at what point, an EUA might be appropriate. While we are encouraged to see the rapid development of potential therapies for COVID-19, in most cases, the effectiveness of novel or repurposed therapies is unknown at the pre-IND stage. Authorization of drugs through the EUA mechanism involves an understanding that the known and potential benefits outweigh the known and potential risks of the drug for the diagnosis, treatment, or prevention of an appropriate disease or condition.⁹ In general, drugs being studied for treatment or prevention of COVID-19 have insufficient data for FDA to make such a determination. Accordingly, many drugs proposed for use under EUAs will more appropriately be the subject of INDs, with consideration regarding potential authorization under the EUA mechanism to follow as appropriate and warranted as more information is available.

B. General Content

FDA recommends sponsors include the following content, and address the following issues, when developing pre-IND meeting requests that will support clinical development programs:

- Drug name.
- Description of the active ingredient, including its physical, chemical, and/or biological characteristics and its source (e.g., synthetic, fermentation, animal derived, plant derived, biotechnology derived). For FDA-approved drugs, current labeling can address this request.
- Brief description of the manufacturing scheme for the active pharmaceutical ingredient and formulation for clinical study.
- The proposed indication (treatment, prevention, specific populations).
- Dosage form, dosing schedule, formulation, and route of administration.
- Known or suspected mechanism of action of the drug.
- Summary of the available pharmacokinetic information.
- Summary of the data and literature supporting the proposed use of the drug for treatment or prevention of COVID-19.
- Summary of the available nonclinical pharmacology and toxicology data (see section IV.C., General Nonclinical Considerations).
- Clinical information to support the proposed trial (see section IV.C., General Clinical Considerations).

⁹ For additional information see the guidance for industry and other stakeholders *Emergency Use Authorization of Medical Products and Related Authorities* (January 2017).

C. General Nonclinical Considerations

FDA recommends the sponsor include certain data and information that allows FDA to evaluate the risks of the investigational drug, including information about the formulation, and appropriate nonclinical studies. Such information will be required for initiation of studies under an IND.¹⁰ For approved drugs, reference to FDA-approved labeling may suffice in some cases. FDA may exercise some flexibility in the types and amount of data necessary to support drug development for treatment or prevention of COVID-19, but for proposals to proceed — when involving unapproved drugs, new doses or formulations of an approved drug, or new routes of administration (e.g., inhalation) that have never been administered to humans — typically nonclinical in vivo data will be needed to determine the risks of the drugs and to support safe starting doses in humans. We recommend that the sponsor include the following in a pre-IND meeting request:¹¹

- A summary of the available nonclinical pharmacology and toxicology data. The summary should include the results of in vitro and in vivo studies conducted with the proposed drug substance and provide a brief summary of study methodology as warranted. The summary should also address the safety of any novel drug excipients. For approved drugs, FDA-approved labeling can be referenced; for drugs under clinical development for other uses, the sponsor may incorporate relevant information through an authorized cross-reference to an existing IND.
- The proposed duration of the clinical trial, in general, supported by nonclinical animal studies of equivalent duration.¹² Such nonclinical animal studies should include standard toxicology and toxicokinetic endpoints, as appropriate. The sponsor should provide an evaluation of the potential for reversibility when there is severe toxicity observed in a nonclinical study with potential adverse clinical effect. Pivotal nonclinical safety studies should be conducted according to good laboratory practices (GLPs).
- The intended route of administration in the clinical trial, which should be the same as was used in the nonclinical animal studies.
- The drug substance and formulation used in nonclinical studies

For small molecule drugs: A battery of nonclinical studies to support a first-in-human (FIH) trial should include assessment of standard safety pharmacology studies (e.g., cardiovascular,

¹⁰ 21 CFR 312.22 and 312.23.

¹¹ For recommendations on the substance and scope of nonclinical studies to support clinical trials for cellular and gene therapy products, see the guidance for industry *Preclinical Assessment of Investigational Cellular and Gene Therapy Products* (November 2013).

¹² We support the principles of the 3Rs (reduce/refine/replace) for animal use in testing when feasible. FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, validated, and feasible. FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

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respiratory, and central nervous system assessments) but can be incorporated into general toxicology studies. In general, FDA expects a pre-IND meeting request for a small molecule drug to include data from general toxicology studies in two species (at least one nonrodent) and genetic toxicology, including an Ames reverse mutation assay and a second in vitro assessment. The drug substance used in the toxicology studies should be identical to that proposed for clinical investigation.

For biological products: A battery of nonclinical studies to support a FIH trial should include assessment of applicable safety pharmacology studies (e.g., cardiovascular, respiratory, and central nervous system assessments) but can be incorporated into the general toxicology study. In general, in vivo studies should be conducted, and will include one general toxicology study in a relevant species and a tissue cross-reactivity assay in human tissues when indicated and technically feasible. When indicated, sponsors should consider studies that assess enhanced potential for toxicity in an animal model of infection. The drug product that is used in the definitive pharmacology and toxicology studies should be comparable to the product proposed for the initial clinical studies.

D. General Clinical Considerations

We recommend that sponsors developing drugs for treatment or prevention of COVID-19 include in their pre-IND meeting requests the items identified below. For additional information on clinical endpoints in COVID-19 development programs, we recommend reviewing the guidance for industry *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention* (May 2020).

- The submission should include a detailed justification for the proposed dose, dosing range, number of doses, and dose interval, and route of administration for use in the treatment or prevention of COVID-19. This justification should consider the identified toxicological profile and resulting safety margins compared to the proposed clinical doses.
- The submission should include a summary of the drug's safety data with previous human experience in other studied populations or indications (e.g., exposure, adverse events, serious adverse events, if available).
- We strongly recommend that for phase 2 or 3 trials, the sponsor propose a randomized, placebo-controlled, double-blind clinical trial using a superiority design. The variability of clinical course of COVID-19 following treatment or prophylaxis and the incomplete understanding of this newly recognized disease can seriously affect the reliability of any conclusions based on uncontrolled data. The sponsor should submit with the pre-IND meeting request a draft protocol that includes phase of development, mechanism of action, overall design, subject population with inclusion and exclusion criteria, endpoint(s), safety assessments, and brief statistical considerations.

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- In general, to be meaningful, proposed clinical endpoints should reflect an improvement in how a trial subject feels, functions, or survives. The chosen endpoints should reflect the severity of the population being studied.
- The size of the proposed trial should depend on the selected endpoint, anticipated treatment effect, assumptions of the rate in the population intended for study (e.g., various prophylaxis or treatment populations with different event rates and levels of risk), and the safety profile of the drug. Other considerations for sponsors include whether the drug is an already FDA-approved drug for another indication that the sponsor proposes to repurpose for use in treatment or prevention of COVID-19 and for which the sponsor already has relevant safety data at the proposed dose, or a new drug with limited human safety data.
- The submission should include a detailed safety monitoring plan. There are significant safety concerns in the COVID-19 patient population, both because of risks associated with the disease and because of the potential for adverse events from the treatment that might be difficult to recognize. We recommend the use of an independent data monitoring committee (DMC).¹³ Sponsors should ensure there will be appropriate DMC monitoring to ensure subject safety accounting for important factors such as the expected enrollment rate, the expected lag time to analyze interim data for DMC meetings, and the frequency of DMC meetings.
- The submission should include a time and event table, which will include end of trial and follow-up plans as appropriate for the specific investigational drug.

E. General Product Quality Considerations

Sponsors should submit sufficient information to ensure acceptable quality (e.g., identity, purity, strength/potency) of the investigational drug for the intended phase of the drug development. The sponsor should also provide summary data and information supporting that the drug is stable for the duration of the clinical trial.

FDA recommends sponsors take into account the following specific product quality considerations in pre-IND meeting requests, as applicable:¹⁴

- The sponsor should consider whether dosage forms and instructions for use need to be adjusted for any specific limitations that may occur with severe COVID-19 (e.g., administration of oral dosage forms to intubated patients).

¹³ See the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees* (March 2006).

¹⁴ FDA may request additional product, manufacturing, and quality information, taking into account the source, characteristics, and complexity of the drug. In particular, complex biological products may require additional information to support initiation of studies.

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- If the sponsor plans to enroll or treat patients who are intubated in a trial of an oral dosage form, the sponsor should provide details about how the drug will be prepared for administration to patients who are intubated (e.g., via an enteral feeding tube).¹⁵
- If an oral dosage form will be reconstituted into solution or suspension, the sponsor should provide in-use stability data in the IND to support the duration of storage after reconstitution, unless the drug will be administered immediately after preparation.

F. Additional Recommendations for Antiviral Drugs

Investigational antiviral drugs can be identified based on cell culture antiviral activity data (i.e., half maximal effective concentration (EC₅₀) value and therapeutic index) and, preferably, on animal model findings, but these activity data may not reliably predict benefit in human patients. Following characterization of the safety profile of the drug in toxicology and pharmacology studies and early stage clinical trials, the sponsor will need to establish the effectiveness of the drug.¹⁶

We recognize that some sponsors may seek development advice for potential antiviral drugs in very early stages. If the sponsor does not yet have antiviral activity information, but believes the drug may have potential activity against SARS-CoV-2, the sponsor may find it useful to consult the National Institutes of Health (NIH) Division of Microbiology and Infectious Diseases web page,¹⁷ which contains information about preliminary screening activities that may be available to potential sponsors of antiviral drugs.

G. Additional Recommendations for Inhalational Drugs

A pre-IND meeting request for a drug for inhalation (e.g., metered dose inhaler, nebulization) should include data to support use of the proposed drug for this route of administration in humans. Such information includes details of the proposed formulation (including drug product excipients), device for administration, and (as described in section IV.C., General Nonclinical Considerations) GLP toxicology studies with the intended route of administration (inhalation). The GLP toxicology studies should support the proposed dose and duration.¹⁸

¹⁵ See the draft guidance for industry *Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments* (July 2018). When final, this guidance will represent the FDA's current thinking on this topic.

¹⁶ See the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic.

¹⁷ See the NIH's Preclinical and Clinical Services Contacts: Division of Microbiology and Infectious Diseases web page, available at <https://www.niaid.nih.gov/about/dmid-preclinical-clinical-services-contacts>.

¹⁸ For general information, see Tepper, J. S., et al., 2016, Symposium Summary: "Breathe In, Breathe Out, It's Easy: What You Need to Know About Developing Inhaled Drugs," *Int J Toxicol*, 35(4): 376–392.

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V. HOW TO SUBMIT A PRE-IND MEETING REQUEST

Sponsors developing drugs for use in treatment or prevention of COVID-19 have three options for submitting their pre-IND meeting requests:

- **Option 1 (preferred method): Electronic Submissions Gateway (ESG):** ESG is an FDA-wide solution for accepting electronic IND, NDA, abbreviated new drug application (ANDA), or BLA regulatory submissions. The FDA ESG enables the secure submission of premarket and postmarket regulatory information for review.¹⁹
- **Option 2: for CDER pre-IND meeting requests, use NextGen Portal:** The CDER NextGen Portal is a website for users to report information to FDA. Development programs with pre-assigned ANDA, NDA, BLA, IND, and master file numbers can be submitted via the CDER NextGen Portal.²⁰
- **Option 3: for CBER pre-IND meeting requests that cannot be sent through ESG:** send emails to CBERDCC_eMailSub@fda.hhs.gov.

Note: If a sponsor obtains a pre-assigned IND number for a new COVID-19 development program, that number should subsequently be listed on materials (e.g., pre-IND meeting request) the sponsor submits for that program.²¹

VI. ADDITIONAL RESOURCES

For further questions on pre-IND meeting requests and divisional assignments during the COVID-19 public health emergency, sponsors of CDER-regulated drugs should email COVID19-productdevelopment@fda.hhs.gov. For further questions on pre-IND meeting requests and office assignments, sponsors of CBER-regulated drugs should email CBER at CBERProductJurisdiction@fda.hhs.gov. Sponsors that are unsure of whether their drug is CDER- or CBER-regulated should make initial contact for COVID-19 drug development through COVID19-productdevelopment@fda.hhs.gov.

Additional information regarding FDA's response to the COVID-19 public health emergency is available at <https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19>.

¹⁹ See the FDA's ESG web page available at <https://www.fda.gov/industry/electronic-submissions-gateway>.

²⁰ See CDER NextGen Portal web page, available at <http://edm.fda.gov>.

²¹ See the Requesting a Pre-Assigned Application Number web page available at <https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/requesting-pre-assigned-application-number>.