

*Contains Nonbinding Recommendations*

**Protecting Participants in  
Bioequivalence Studies for  
Abbreviated New Drug  
Applications During the COVID-19  
Public Health Emergency**

---

**Guidance for Industry**

**January 2021**

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Generic Drugs**

# 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 webpage 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 email request to [GenericDrugs@fda.hhs.gov](mailto:GenericDrugs@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 FDA's Office of Generic Drugs in the Center for Drug Evaluation and Research at [GenericDrugs@fda.hhs.gov](mailto:GenericDrugs@fda.hhs.gov).

## **Table of Contents**

I.	Introduction.....	1
II.	Background.....	2
	A. Establishing Bioequivalence .....	2
	B. Impact of Current Pandemic .....	3
III.	Discussion.....	4
	A. Safety of Participants .....	4
	1. Eligibility .....	5
	2. Study Visit.....	5
	B. Standard Operating Procedure (SOP) Development and Revision.....	8
	C. Protecting Scientific Validity of BE Studies.....	8
	1. Protocol Amendment and Development .....	9
	2. Deviations .....	9
	3. Study Oversight.....	10
	4. Drug Expirations .....	10
	D. Plan for Timely and Organized Initiation or Resumption of BE Studies.....	10

# Protecting Participants in Bioequivalence Studies for Abbreviated New Drug Applications During the COVID-19 Public Health Emergency

---

## Guidance for Industry

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 staff or 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 recommendations to prospective applicants of abbreviated new drug applications (ANDAs) on ensuring the protection of participants when resuming or initiating bioequivalence (BE) studies conducted to support the approval of an ANDA that have been disrupted during the COVID-19 public health emergency.

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

## *Contains Nonbinding Recommendations*

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.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA 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" (COVID-19). On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.<sup>1</sup> In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.<sup>2</sup>

### **A. Establishing Bioequivalence**

To receive approval for an ANDA, an applicant generally must demonstrate, among other things, that its proposed drug product is bioequivalent to the reference listed drug (RLD).<sup>3</sup> The FD&C Act provides that a generic drug is bioequivalent to the listed drug if:

The rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses.<sup>4</sup>

---

<sup>1</sup> Secretary of Health and Human Services Alex M. Azar II, Determination that a Public Health Emergency Exists (originally issued Jan. 31, 2020, and subsequently renewed), *available at* <https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx>.

<sup>2</sup> Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak (Mar. 13, 2020), *available at* <https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/>.

<sup>3</sup> See section 505(j)(2)(A)(iv) of the FD&C Act (21 U.S.C. 355(j)(2)(A)(iv)) and 21 CFR 314.94(a)(7). In general, to obtain approval of an ANDA for a generic drug, an ANDA applicant first must identify the previously approved drug product it seeks to duplicate (i.e., the RLD), and must show, among other things, that the generic drug is bioequivalent to the RLD. A reference standard (RS) selected by FDA is the specific drug product that the ANDA applicant must use in conducting any in vivo BE testing required to support approval of its ANDA. The RS, selected by FDA, is ordinarily the RLD. For ease of reference, this guidance document will only use the terms *RLD* or *reference product* when describing regulatory requirements and recommendations relating to BE. For more information regarding the distinction between an RLD and RS, see FDA's guidance for industry *Referencing Approved Drug Products in ANDA Submissions* (Oct. 2020). 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>.

<sup>4</sup> Section 505(j)(8)(B)(i) of the FD&C Act. See also section 505(j)(8)(B)(ii) and (C) of the FD&C Act; 21 CFR 314.3(b); 21 CFR 320.1; and 21 CFR 320.23(b).

## *Contains Nonbinding Recommendations*

For most products, the focus of BE studies is on the release of the drug substance from the drug product into the systemic circulation. During such BE studies, an applicant compares the systemic exposure profile of a test drug product to that of the RLD designated in FDA's *Approved Drug Products with Therapeutic Evaluations* (the Orange Book).<sup>5,6</sup>

Under FDA regulations, an applicant must use "the most accurate, sensitive, and reproducible approach available among those set forth" in 21 CFR 320.24(b) to demonstrate BE.<sup>7</sup> As noted in 21 CFR 320.24, in vivo and/or in vitro methods can be used to establish BE. These methods include comparative pharmacokinetic (PK), in vitro tests predictive of human in vivo bioavailability (in vitro-in vivo correlation), pharmacodynamic, clinical endpoint, and in vitro studies.<sup>8</sup>

### **B. Impact of Current Pandemic**

FDA recognizes that the COVID-19 public health emergency may impact the conduct of BE studies in human participants to support demonstration of BE and approval of an ANDA. Public health measures to control the virus have posed challenges to conducting BE studies generally due to travel limitations, study site closures, and laboratory closures. Consequently, BE studies in human participants may have been suspended, resulting in interruptions in the development of study products. These BE studies may have been suspended at various stages ranging from protocol development, recruitment, screening, during a study period, or in between study periods.

Additionally, FDA recognizes the resulting challenges that the generic pharmaceutical industry faces due to the COVID-19 public health emergency and its control measures across the globe. The unexpected disruptions of BE studies have compelled the clinical research industry to find short-term alternative measures while identifying sustainable and feasible long-term solutions. For BE studies with human participants, protecting participant rights, welfare and assuring the quality and integrity of the data while maintaining compliance with all applicable regulatory requirements continue to be the main focus. In addition, the current public health emergency necessitates the consideration of reducing risk of exposure to SARS-CoV-2. The recommendations in this guidance are intended to facilitate the safe conduct of BE studies with human participants during the COVID-19 public health emergency.<sup>9, 10</sup>

---

<sup>5</sup> See 21 CFR 314.3(b) defining reference listed drug and reference standard, 21 CFR 320.24 and FDA's guidance for industry *Referencing Approved Drug Products in ANDA Submissions* (Oct. 2020).

<sup>6</sup> The Orange Book is available at <https://www.accessdata.fda.gov/scripts/cder/ob/>.

<sup>7</sup> 21 CFR 320.24(a).

<sup>8</sup> See 21 CFR 320.24(b).

<sup>9</sup> FDA has issued a number of guidances related to the legal requirement for a generic drug to demonstrate bioequivalence to a reference product, in which we provide both general and product-specific recommendations. See, for example, the draft guidance for industry *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application* (Dec. 2013). When final, this guidance will represent the FDA's current thinking on this topic. See also FDA's Product-Specific Guidances for Generic Drug Development web page, available at <https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development>. We recommend that potential ANDA applicants become familiar with the recommendations regarding BE described in those guidances.

<sup>10</sup> For additional considerations regarding the conduct of bioequivalence studies with human participants during the COVID-19 public health emergency, to the extent they are relevant, see *FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency* (Mar. 2020), updated on Dec. 4, 2020.

### **III. Discussion**

As a general matter, when conducting BE studies to support an ANDA and as described in more detail below, we recommend a careful and methodical approach be implemented to safeguard the health and safety of study participants.

We recommend that applicants consider the potential impact of participation on the participants' health (e.g., the diagnoses of participants in BE studies, comorbidities, etc.) in any particular study. Additionally, we recommend that the safety of study site staff be protected, and care taken to ensure study integrity and scientific validity of the data generated due to modifications to study conduct or design. Accordingly, we recommend that sites develop site-specific plans for the resumption or initiation, as appropriate, of safe, timely, and organized BE studies.<sup>11</sup>

ANDA applicants must provide adequate information in their submission related to any disruption in their BE studies or deviation from study protocols associated with the COVID-19 public health emergency, even when such deviations are made in connection with recommendations from FDA.<sup>12</sup> Ultimately, whether the Office of Generic Drugs will receive an ANDA for substantive review will be determined during the filing review.<sup>13</sup> The acceptability of a BE study supporting the application will be determined during the scientific assessment of an ANDA.<sup>14</sup>

#### **A. Safety of Participants**

BE studies conducted during the development of generic drugs often involve healthy participants.<sup>15</sup> Given the COVID-19 public health emergency, the Agency recognizes the importance of developing additional recommendations for procedures to ensure the safety of the healthy participants who are enrolled in studies to support ANDAs as well as the safety of participants in the patient population for which the reference product is indicated<sup>16</sup> for the subset of BE programs in which a healthy population is not indicated. Resumption and initiation of BE studies should follow applicable (national or local) guidelines and requirements to control the spread of the virus.<sup>17</sup>

---

<sup>11</sup> See the CDC's website on Interim Infection Prevention and Control Recommendations for Healthcare Personnel During the Coronavirus Disease 2019 (COVID-19) Pandemic, available at <https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-recommendations.html>.

<sup>12</sup> See 21 CFR 314.94(a)(7); see also guidance for industry *ANDA Submissions – Content and Format of Abbreviated New Drug Application* (June 2019). For BE studies subject to the requirements of 21 CFR Part 312, protocol amendments and information amendments must also be submitted as required by 21 CFR 312.30 - .31. For FDA's general advice to sponsors on managing protocol deviations and amendments to ongoing clinical trials during the COVID-19 public health emergency see Q3 of the guidance for industry entitled *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency*.

<sup>13</sup> See 21 CFR 314.101(b)(1).

<sup>14</sup> See section 505(j)(4)(F) of the FD&C Act (21 USC 335(j)(4)(F)) and 21 CFR 314.105(c)-(d).

<sup>15</sup> See 21 CFR 320.26(a) stating as part of the guidelines on the design of in vivo bioequivalence studies that testing is conducted in normal adults. Additionally, see generally, 21 CFR part 50 for FDA's regulations on the safety of human participants.

<sup>16</sup> In general, most BE studies utilize healthy subjects as participants, but for products that have toxicity considerations, sometimes a population of participants with symptoms similar to the patient population for which the reference product is indicated. See 21 CFR 320.25(a)(2). In places where comments apply to both, we have used the term *participants*.

<sup>17</sup> See, for example, information on managing healthcare facility operations during the COVID-19 pandemic on the CDC's website on U.S. Healthcare Facilities, available at <https://www.cdc.gov/coronavirus/2019-ncov/hcp/preparedness-checklists.html>.

## *Contains Nonbinding Recommendations*

### *1. Eligibility*

Certain populations may be more susceptible to adverse clinical outcomes from COVID-19 due to age or other comorbid conditions; corresponding information on risks for susceptible populations can be found at the CDC website (<https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/index.html>).

#### a. Inclusion Criteria

Careful selection of a participant population can help minimize risk of transmission of SARS CoV-2 in the participant population. As an overall enrollment strategy, consideration should be given to local prevalence of COVID-19, as well as the availability of diagnostic testing.

#### b. Exclusion Criteria

In general, exclusion criteria should consider relevant comorbidities including a history of significant cardiovascular and respiratory conditions and history or risk of other medical conditions (e.g., diabetes, obesity, chronic kidney disease).

If a BE study is being conducted in participants in the patient population for which the reference product is indicated in line with recommendations in a product-specific guidance, there may be unique considerations that inform whether applicants should utilize the safety considerations recommended in this guidance or make other modifications to accommodate for additional clinically relevant needs of the specific participant population. In the absence of a product-specific guidance addressing participant population safety concerns, FDA recommends implementation of the safety considerations described in this guidance for all study participants, as appropriate unless further modifications are needed to account for vulnerabilities in the specific population participating in the BE study. Additionally, you are encouraged to contact FDA<sup>18</sup> to discuss specific safety concerns for proposed study participants.

### *2. Study Visit*

Prior to the initiation or resumption of BE studies, study sites should adapt screening, admission, and conduct procedures to minimize exposure to SARS-CoV-2 during the current public health emergency.<sup>19</sup>

#### a. Consenting and/or Screening

Study site standard operating procedures (SOPs) should include consideration of methods to reduce the amount of time spent by the study participant at the study site and any interactions with other

---

<sup>18</sup> For specific questions related to generic drug development, submit a controlled correspondence or pre-ANDA meeting request, as appropriate. See the guidances for industry *Controlled Correspondence Related to Generic Drug Development* (Dec. 2020) and *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (Nov. 2020).

<sup>19</sup> See footnote 11.



## *Contains Nonbinding Recommendations*

participants and site staff, including the use of “electronic informed consent (eIC).”<sup>20</sup> If eIC is unavailable, alternative methods of obtaining informed consent other than face-to-face consent interviews may be acceptable if those methods allow for an adequate exchange of information and documentation and ensure that the signer of the consent form is the person who plans to enroll as a participant in the study or is the legally authorized representative of the participant.<sup>21</sup>

Prospective applicants should consult or ensure that any party conducting BE studies on its behalf consults with infectious disease and public health experts to implement additional procedures to minimize risk of transmission between participants and staff. Such approaches may include symptom screening prior to visiting the study site and work flow adjustments to limit the frequency of close contacts between BE study participants and staff or among participants.<sup>22</sup>

### b. COVID-19 Infection Mitigation Models

To minimize risks of exposure for participants and staff, we recommend two alternative approaches described below. Depending upon the pharmacokinetic profile of the drug(s) being studied, consideration should be given to employing a combination of the two approaches. The following subsections provide examples of two possible approaches that may assist prospective applicants but note that the recommendations provided may not address all situations.

#### i. Example 1: Confinement (Bubble) Design

**Summary:** Participants, and potentially site staff, are confined to the facility for the duration of the study (i.e., from the beginning of screening until completion of study) with no ambulatory visits. It is expected that this would limit participant and staff infection from sources outside the facility once they are enrolled and confined to the facility. In general, a site following Example 1 would implement regular temperature checks and COVID-19 symptom screening for participants and staff, would ensure participants and staff wear appropriate personal protective equipment<sup>23</sup> and practice hand sanitization methods, and would perform sampling at the bedside of each participant. Example 1 may, however, result in the possibility of infection being transmitted within the facility and may subject staff to sequestration or screening upon entrance to and exit from the study environment. Other operating procedures should be undertaken to assure the safety of participants and staff. Consultation with infection control experts and/or public health guidelines can inform such procedures.

---

<sup>20</sup> See the guidance for institutional review boards, investigators, and sponsors *Use of Electronic Informed Consent in Clinical Investigations – Questions and Answers* (December 2016). As used in that guidance document, “electronic informed consent” refers to the use of electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, passive and interactive web sites, biological recognition devices, and card readers, to convey information related to the study and to obtain and document informed consent.

<sup>21</sup> See 21 CFR 50.20 and 50.27(a). See also the guidance for institutional review boards, investigators, and sponsors *Use of Electronic Informed Consent Questions and Answers* (Dec. 2016).

<sup>22</sup> See footnote 11.

<sup>23</sup> See the CDC’s website on Using Personal Protective Equipment, *available* at <https://www.cdc.gov/coronavirus/2019-ncov/hcp/using-ppe.html>.

## *Contains Nonbinding Recommendations*

### ii. Example 2: Non-Confinement (Ambulatory) Design

**Summary:** Participants are not confined at the facility for the duration of the study (i.e., no overnight stays). This design uses select timepoints for PK sampling that allows the participant to travel to and from the site each day. It is expected that this design would minimize the participant's possible exposure to infection from sources within the facility from what otherwise could be long periods of confinement with other participants. In general, a site following Example 2 would implement regular temperature checks and COVID-19 symptom screening for each ambulatory visit, ensure that one participant's visit does not overlap with the visit of another study participant, and would only assign one participant per room for blood collection, for example, and would disinfect the room once the participant leaves.<sup>24</sup> Example 2 may, however, result in increased risk of infection from sources external to the site.

### 3. *Sampling*<sup>25</sup>

#### a. Alternative PK Approach

One approach to reduce participant/staff exposure to COVID-19 is to reduce the number of visits by using alternative PK modeling approaches to optimize PK sampling time points. Given that some information on the PK profile is available for the RLD, using that information and leveraging PK modeling methods, the goal of alternative PK approaches is to minimize time points that require repeat ambulatory visits. Where applicable, use of modeling or PK parameters (such as partial area under the curve (pAUC)) can be investigated by the applicant, and the acceptability of these may be considered by FDA to establish BE between an RLD and a generic drug without compromising on quality of the data.<sup>26</sup>

#### b. Spaced Dosing and Sampling

Another method to reduce exposure between participants is by scheduling the participant visits such that the visits do not overlap. Spacing the initial dosing visit for each participant would ensure that the subsequent visits would be similarly spaced out from the dosing visit. Alternative PK approaches to increase the visit window for ambulatory visits would also provide flexibility for the site staff to schedule the ambulatory sampling visits such that they do not overlap. This method, however, might extend the duration of the study, and should include appropriate prespecified statistical considerations described clearly within the statistical analysis plan, to address group effect and minimization of potential bias.

---

<sup>24</sup> See footnote 11.

<sup>25</sup> For additional questions related to the approaches described in this section, we recommend that prospective applicants submit specific questions related to their impacted bioequivalence studies, including questions about protocol revisions and information collection, via the controlled correspondence process (see footnote 18). As appropriate, please provide detailed information including your proposed plans, rationale, and justification supporting your proposal.

<sup>26</sup> Applicants should provide justification that the proposed approach does not compromise the accuracy, reproducibility, and sensitivity of the BE test.

## *Contains Nonbinding Recommendations*

### c. Off-Site (At-Home) Sampling

To reduce participant-to-participant or participant-to-staff interactions, performing the PK sampling at home may be explored as a suitable alternative method.<sup>27</sup> As is generally the case, we recommend that validation for an alternative method follow the agency's recommendations in FDA's guidance for industry *Bioanalytical Method Validation* (May 2018), including demonstration that the data be accurate, reliable and reproducible. In addition, a correlation study should be performed to assure that samples collected at home would provide the same results as the whole blood samples taken at the site. Because at-home sampling methodologies are not standardly-applied methodologies, we recommend consulting with the Agency prior to utilizing these methodologies and providing scientific justification to FDA in any ANDA submission.<sup>28</sup> Micro-sampling has gained interest as a participant-centric approach in the last decade. Commercially available dry blood spots and micro sampling kits, initially developed for therapeutic drug monitoring, may enable home sampling, significantly reducing the risk of exposure to SARS-CoV-2. However, there are some potential challenges with this approach that should be considered, including participant identity verification, sampling time confirmation, and bioanalytical method development and validation.

### d. Follow-Up

Steps taken to reduce the amount of non-essential time spent at the site may also be leveraged to eliminate the need for the in-person follow-up visit. For example, site staff may perform End-of-Treatment procedures at the time of discharge, and a follow-up visit may be conducted virtually (video or phone call), unless the participant has experienced adverse events that should be investigated via a physical exam.

## **B. Standard Operating Procedure (SOP) Development and Revision**

Prior to formally initiating, reopening, and/or resuming study activities, all sites should develop a detailed plan or SOP on how to mitigate risks of exposure to the virus as well as protect participants and study staff while maintaining study integrity. Consultation with local and Federal guidelines for infection control in business and health care settings is recommended.<sup>29</sup>

## **C. Protecting Scientific Validity of BE Studies**

As noted above, FDA recognizes the challenges that the generic pharmaceutical industry faces due to the COVID-19 public health emergency and the unexpected disruptions of BE studies. The following considerations in this section are provided to help applicants protect participant rights, welfare and assure the quality and integrity of the data while maintaining compliance with all

---

<sup>27</sup> Off-site sampling includes at-home sample collection, such as the participant personally collecting the sample and mailing it in, study personnel picking the sample up from the home, or study personnel coming to the home to collect the sample.

<sup>28</sup> See footnote 18 for information on submitting questions related to generic drug development to the Agency.

<sup>29</sup> See, for example, CDC recommendations on business and workplaces, available at <https://www.cdc.gov/coronavirus/2019-ncov/community/organizations/businesses-employers.html>, and the CDC website on Interim Infection Prevention and Control Recommendations for Healthcare Personnel During the Coronavirus Disease 2019 (COVID-19) Pandemic, available at <https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-recommendations.html>.

## *Contains Nonbinding Recommendations*

applicable legal requirements.

### *1. Protocol Amendment and Development*

Changes in a protocol are typically not implemented before review and approval by the institutional review board (IRB)/independent ethics committee (IEC), and for those BE studies conducted under IND, by FDA.<sup>30</sup> Study sponsors, prospective applicants, and clinical investigators are encouraged to engage with IRBs/IECs and, as applicable, FDA as early as possible when urgent or emergent changes to the protocol or informed consent are anticipated as a result of COVID-19. Such changes to the protocol or investigational plan that are necessary to eliminate immediate hazards to research participants may be implemented prior to IRB review and approval or before filing an amendment to the Investigational New Drug (IND) application, if applicable, but all protocol changes must be reported afterward<sup>31</sup> and should be reported in the ANDA with sufficient information and justification.<sup>32</sup>

The protocol should prospectively identify how the study will handle participant illness (either from COVID-19 or some other reason) during the conduct of the study (e.g., consider whether to remove, replace, or provide another method to address missing data for that participant).

Protocol and statistical analysis plan changes should be made prior to data lock and unblinding; for example, the protocol should prospectively state how missing data will be handled in the statistical analyses and provide appropriate justification for the method chosen. Detailed information about the missing data (i.e., missing drug administration or outcome measurements including, for example, PK measurements), should be collected at the participant level. This information should describe the context for the missing data and how it is related to COVID-19, if applicable, and should be accompanied with adequate justification so that the missing data do not lead to biased equivalence determination. Detailed information for all participants who are discontinued from the study should be provided.

### *2. Deviations*

FDA acknowledges that the COVID-19 public health emergency has led to various deviations and other challenges. For example, contingency measures may have been necessitated by government-level measures to control the virus and additional actions to maintain safety and public health may have been implemented prior to approval of protocol modifications, thereby leading to unavoidable protocol deviations. Good documentation practice for protocol deviations plays a key role, especially during the evolving public health emergency.<sup>33</sup> In addition, keeping a frequent, open line of communication among the study sponsors, monitors, investigators and IRBs/IECs is important.

---

<sup>30</sup> See 21 C.F.R. 320.31; see also 21 C.F.R. 56.109, 312.30-31.

<sup>31</sup> See 21 CFR 56.108(a)(4), and 21 CFR 312.30(b)(2)(ii) (for studies conducted under an IND).

<sup>32</sup> See 21 CFR 314.94(a)(7); see also guidance for industry *ANDA Submissions – Content and Format of Abbreviated New Drug Application* (June 2019).

<sup>33</sup> See 21 CFR 314.94(a)(7); see also guidance for industry *ANDA Submissions – Content and Format of Abbreviated New Drug Application* (June 2019). For BA/BE studies subject to the requirements of 21 CFR Part 312, see also 21 CFR 312.23(a)(6)

## *Contains Nonbinding Recommendations*

### 3. *Study Oversight*

The impact of travel restrictions implemented by government authorities and local institutions on study oversight poses a challenge to site monitoring and quality control/assurance and may lead to the reevaluation of monitoring practice. Remote monitoring may provide more flexibility for BE studies where possible.<sup>34</sup>

When BE studies are conducted at a single location in a country, a decentralized monitoring workforce might aid in a seamless resumption of the studies as public health control measures permit. Hiring local monitors would eliminate the need for air travel, and the impact of travel restrictions between regions or countries would be minimized.

### 4. *Drug Expirations*

In general, when conducting a BE study we do not recommend use of expired reference product or test product which is out of specification due to aging. Prospective applicants may submit questions related to the use of expiring drug products through controlled correspondences (e.g., what alternatives to use of expired drug product might be feasible).<sup>35</sup>

## **D. Plan for Timely and Organized Initiation or Resumption of BE Studies**

Study sites should comply with applicable (national or local) public health guidelines and requirements to control the virus, including state reopening plans for business and healthcare facilities, when deciding on when to reopen facilities and resume human participant BE studies.

As sites plan for resumption or initiation of new BE studies, they should consider the safety of participants and staff. Sites that are better prepared to follow the recommendations provided in this guidance may be better prepared to resume or begin the conduct of BE studies.

---

<sup>34</sup> Remote monitoring is discussed in greater detail in the guidance for industry, investigators, and institutional review boards *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency* (Mar. 2020), updated on Sept. 21, 2020, and the guidance for industry *Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring* (Aug. 2013).

<sup>35</sup> See footnote 18 for information on submitting questions related to generic drug development to the Agency.