



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

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Mitch Frost, MD

Acting Deputy Director
CDER/OGD/ORS/DTPII

CDER | U.S. FDA

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Learning Objectives

- List the elements of study conduct to be considered when planning to resume or initiate new studies with human participants
- Describe how study sites should develop or revise procedural documents while taking the risk for COVID-19 into consideration
- Identify strategies to protect the scientific validity of bioequivalence (BE) studies
- Explain how study sites should best plan for timely and organized resumption of BE studies



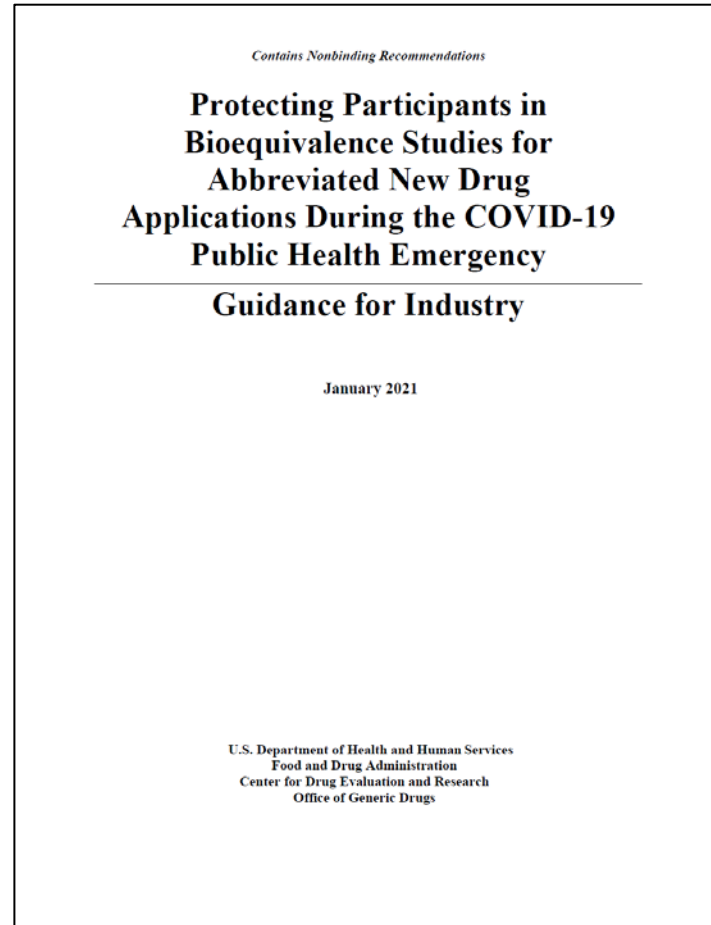
Introduction

- The American public depends on continued access to lifesaving medicines
- Nine out of 10 prescriptions in the U.S. are filled by generic drugs
- The worldwide COVID-19 pandemic created additional complexities, new realities, and unique challenges for all
- During the pandemic, FDA's generic drug program continued its unwavering efforts to help increase the availability of safe, effective, high-quality, more affordable drugs in the U.S.



Introduction (cont.)

- FDA has issued this guidance as part of our commitment to provide timely guidance to support response efforts to the COVID-19 pandemic
- This policy is intended to remain in effect only for the duration of the public health emergency due to COVID-19



Background

- 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
- The impact may be due to travel limitations, study site closures, and laboratory closures
- Consequently, BE studies in human participants may have been suspended at various stages ranging from protocol development, recruitment, screening, during a study period, or in between study periods



Background (cont.)

- 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 legal requirements continues to be paramount
- 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
- 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

Safety of Participants



- Eligibility
 - Some at greater risk than others for severe illness due to COVID-19¹
 - Inclusion Criteria – enrollment strategy should consider local prevalence
 - Exclusion Criteria – consider relevant comorbidities and study population (healthy participants versus patients)

Safety of Participants (cont.)



- Study Visit
 - Aim should be to minimize exposure to SARS-CoV-2
 - Consenting and/or Screening
 - Considerations to implement methods to reduce participants time at the site and their interactions with other participants and site staff
 - Electronic informed consent² or other methods to avoid obtaining face-to-face informed consent
 - Consult with experts to implement additional procedures to minimize risk³

Safety of Participants (cont.)



- Study Visit (cont.)
 - Examples of COVID-19 Infection Mitigation Models
 - Example 1: Confinement (Bubble) Design
 - Participants, and potentially site staff, are confined to the facility for the duration of the study
 - Regular temperature checks and COVID-19 symptom screening for participants and staff
 - Ensure participants and staff wear appropriate personal protective equipment,⁴ practice hand sanitation, and perform sampling at bedside

Safety of Participants (cont.)

- Study Visit (cont.)
 - Examples of COVID-19 Infection Mitigation Models (cont.)
 - Example 2: Non-Confinement (Ambulatory) Design
 - No overnight stays at the facility
 - Uses select timepoints for pharmacokinetic (PK) sampling
 - Minimizes participants risk for exposure to infection from sources within the facility

Safety of Participants (cont.)



- Study Visit (cont.)
 - Sampling
 - Alternative PK Approach
 - Alternative PK modeling approaches to optimize PK sampling time points
 - Goal is to minimize time points that require repeat ambulatory visits
 - Acceptability may be considered by FDA and applicants should provide justification that accuracy, reproducibility, and sensitivity of the BE test are not compromised

Safety of Participants (cont.)

- Study Visit (cont.)
 - Sampling (cont.)
 - Spaced Dosing and Sampling
 - Scheduling of participants such that visits do not overlap
 - May extend the duration of the study
 - Statistical considerations to control for group effect and to minimize other potential sources of bias should be prespecified and clearly described within the statistical analysis plan

Safety of Participants (cont.)



- Study Visit (cont.)
 - Sampling (cont.)
 - Off-Site (At-Home) Sampling
 - Examples include participants collecting samples and mailing, study personnel picking up, or study personnel coming to the home for sample collection
 - Dry blood spots and micro sampling kits may enable home sampling
 - Validation for an alternative method should follow FDA’s guidance recommendations⁵
 - 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



Safety of Participants (cont.)

- Study Visit (cont.)
 - Sampling (cont.)
 - Follow-Up
 - Strategies to reduce in-person follow-up visits might include performing End-of-Treatment procedures at the time of discharge and subsequent follow-up visits may be conducted virtually
 - However, this does not preclude the need for investigation via a physical exam for those participants who have experienced adverse events



Standard Operating Procedures (SOP)

- Prior to formally initiating, reopening, and/or resuming study activities, all sites should:
 - Develop a detailed plan or SOP
 - Approaches to mitigate risks of exposure to the virus
 - 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 recommended⁶

Protecting Scientific Validity

- Protocol Amendment and Development
 - Those sponsoring and/or conducting studies are encouraged to engage with institutional review boards (IRB)/independent ethics committees (IEC) 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 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
 - Handling of participant illness (either from COVID-19 or some other reason) should be prespecified
 - Protocol and statistical analysis plan changes should be made prior to data lock and unblinding

Protecting Scientific Validity (cont.)



- Deviations

- FDA acknowledges that the COVID-19 public health emergency has led to various deviations and other challenges that may have been implemented prior to approval of protocol modifications, thereby leading to unavoidable protocol deviations
- Good documentation practice for protocol deviations is critical
- Additionally, a frequent and open line of communication among the study sponsors, monitors, investigators and IRBs/IECs is important

Protecting Scientific Validity (cont.)



- Study Oversight

- Travel restrictions implemented by government authorities and local institutions may pose a challenge to site monitoring and quality control/assurance
- Remote monitoring may be considered⁷
- When studies are conducted at a single location, local monitors could help eliminate the need for air travel and the impact of travel restrictions between regions or countries would be minimized

Protecting Scientific Validity (cont.)



- Drug Expirations

- In general, use of expired reference product or test product which is out of specification due to aging is not recommended⁸
- 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)

Plan for Resumption of Studies



- When planning to reopen facilities and resume or initiate new human participant 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
 - 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

Question #1

Which of the following are examples of COVID-19 infection mitigation models?

- a. Confinement (Bubble) Design
- b. Containment (Sanitization) Design
- c. Non-Confinement (Ambulatory) Design
- d. a and c
- e. All of the above



Question #2

Protocol revisions or modifications made while conducting a study during the COVID-19 pandemic do not need to be reported to the IRB/IEC.

- a. True
- b. False

Resources

1. See the CDC's website on Different Groups of People at Increased Risk for Severe Illness <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/index.html>.
2. 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.
3. 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>.
4. See the CDC's website on Using Personal Protective Equipment, *available at* <https://www.cdc.gov/coronavirus/2019-ncov/hcp/using-ppe.html>.
5. See the guidance for industry [*Bioanalytical Method Validation \(May 2018\)*](#)
6. 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>.



Resources

7. Remote monitoring is discussed in greater detail in the guidance for industry, investigators, and institutional review boards [*Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency \(March 2020\)*](#), updated on January 27, 2021, and the guidance for industry [*Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring \(August 2013\)*](#).
8. See the guidance for industry [*Development of Abbreviated New Drug Applications During the COVID-19 Pandemic – Questions and Answers \(April 2021\)*](#).



Closing Thought

Adherence to the principles of good clinical practice, including human subject protection, is universally recognized as a critical requirement to the ethical conduct of research involving human subjects*

*FDA website *Clinical Trials and Human Subject Protection*



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