# Nonclinical Considerations for Mitigating Nonhuman Primate Supply Constraints Arising from the COVID-19 Pandemic

## Guidance for Industry

**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)**
**Oncology Center for Excellence (OCE)**

**February 2022**
**Pharmacology/Toxicology**

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# 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-2021-D-1311 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 web page 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 document number FDA-2021-D-1311 and complete title of the guidance in the request.

## Questions

For questions about this document, contact (CDER) Ronald Wange at 301-796-1304, Ronald.Wange@fda.hhs.gov, or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

# Table of Contents

*Contains Nonbinding Recommendations*

# Nonclinical Considerations for Mitigating Nonhuman Primate Supply Constraints Arising from the COVID-19 Pandemic Guidance for Industry[1]

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 help sponsors mitigate the challenges related to the constrained supply of nonhuman primates (NHPs) available for conducting nonclinical toxicity assessments, which has arisen as a consequence of the current COVID-19 pandemic.

This guidance is intended to remain in effect for the duration of the public health emergency related to COVID-19 declared by the Department of Health and Human Services, including any renewals made by the Secretary in accordance with section 319(a)(2) of the Public Health Service Act (42 U.S.C. 247d(a)(2)). However, the recommendations and processes described in the guidance are relevant to help mitigate the constrained supply of NHPs for nonclinical toxicity assessments that are expected to persist beyond the termination of the COVID-19 public health emergency and reflect the Agency's current thinking on this issue. Therefore, within 60 days following the termination of the public health emergency, FDA intends to revise and replace this guidance with any appropriate changes based on comments received on this guidance and the Agency's experience with implementation.

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

[1] This guidance has been prepared by the Office of New Drugs in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research and the Oncology Center for Excellence at the Food and Drug Administration.

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.

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 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" (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.[2] In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.[3]

During the COVID-19 pandemic, there has been a reduction in the supply of NHPs available for conducting nonclinical toxicity assessments. In conjunction with this reduction in supply, there has been a substantial increase in the demand for NHPs for the testing of investigational COVID-19 treatments and vaccine candidates. This reduction in supply and the prioritization for COVID-19-related studies have severely restricted the availability of NHPs for other pharmaceutical development programs, resulting in a disruption in supply that has the potential to significantly delay the development of new medications for the treatment of diseases currently without effective treatment options. Though the disruption affects the NHP supply generally, there is a particularly acute shortage of sexually mature NHPs that are often the only pharmacologically relevant species with which to assess developmental and reproductive toxicity endpoints for biotherapeutic proteins (biological products).

[2] Secretary of Health and Human Services, Determination that a Public Health Emergency Exists. (originally issued January 31, 2020), *available at* https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx.

[3] Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak (March 13, 2020), *available at* https://trumpwhitehouse.archives.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/. On February 24, 2021, there was a Presidential Declaration continuing the national emergency concerning the COVID-19 pandemic beyond March 1, 2021. See Continuation of the National Emergency Concerning the Coronavirus Disease 2019 (COVID-19) Pandemic (February 24, 2021), available at https://www.federalregister.gov/documents/2021/02/26/2021-04173/continuation-of-the-national-emergency-concerning-the-coronavirus-disease-2019-covid-19-pandemic.

## III. DISCUSSION

### A. NHP Use in General Toxicology Studies

Sponsors should consider many factors when choosing the appropriate species for assessing pharmaceutical safety in an animal toxicology study; it is up to the sponsor to select the appropriate species based on predictability to the human response.[4, 5] These factors may include metabolic, pharmacokinetic, and pharmacologic similarities to humans as well as sensitivity to particular types of toxicity, among other factors. Many biological products are designed to engage human targets with high specificity. As a consequence, biological products typically only manifest their intended pharmacological activity in other primates, often making NHPs the only animal species that allows for toxicity testing of the biological product that is intended to be used in humans. There are instances, however, in which a biological product may be pharmacologically active in other species. For the duration of the COVID-19-related disruption in the supply of NHPs, sponsors should consider the following when planning nonclinical approaches to address the safety of biological products:

- If the biological product is active in other nonrodent species, the sponsor should conduct any warranted general toxicity studies in a nonrodent species other than the NHP, whenever scientifically justified.

- On a case-by-case basis, if the biological product is active in a rodent and acts on a well-characterized target (e.g., vascular endothelial growth factor, or its receptor), it may be scientifically appropriate for sponsors to conduct warranted general toxicity studies only in the rodent.

For small molecule drug development programs, the NHP is generally not the only relevant nonrodent species. For the duration of the COVID-19-related disruption in the supply of NHPs, sponsors should consider the following when planning approaches to nonclinically address the safety of small molecule drugs:

- We discourage the use of NHPs for the general toxicology assessment of small molecule drugs, unless the sponsor can provide a scientifically compelling reason why NHPs must be used.

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[4] FDA has provided recommendations regarding appropriate species selection in multiple guidance documents. See, for example, the International Council for Harmonisation (ICH) guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012) (ICH S6(R1)), the guidance for industry *Preclinical Assessment of Investigational Cellular and Gene Therapy Products* (November 2013), and the guidance for industry *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers* (July 2005). 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.

[5] FDA supports the principles of the 3Rs, to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if they wish to use a nonanimal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method is adequate to meet the regulatory need.

- Sponsors should not use sexually mature NHPs in toxicity studies designed specifically to assess fertility by histopathological examination when fertility parameters can be assessed in rodents.

### B. NHP Use in Developmental and Reproductive Toxicity Assessments

#### *1. Small Molecule Drugs*

Consistent with current FDA guidance on the assessment of developmental and reproductive toxicity (DART),[6] FDA considers NHPs to be a nonroutine test species for the DART assessment of small molecule drugs. FDA strongly discourages sponsors from using NHPs for assessing DART endpoints for their small molecule drug development programs.

#### *2. Biological Products*

Consistent with current FDA guidance,[7] sponsors should only use NHPs for the DART assessment of biological products if they are the only relevant species. For the duration of the COVID-19-related disruption in the supply of NHPs, sponsors should also consider the following when planning approaches to address DART for biological products that are pharmacologically inactive in nonprimates:

- Although the stated preference of ICH S6(R1)[8] is for testing the clinical candidate (in the NHP), while the supply of NHPs is disrupted, we strongly encourage the use of appropriate alternative models for assessing DART endpoints (e.g., species-specific surrogates in rodents, genetically modified rodents) when scientifically justified.

- On a case-by-case basis, a sponsor can consider conducting a DART assessment solely using a weight-of-evidence approach. Typically, FDA would consider this approach to be scientifically justified only in instances where strong scientific evidence indicates risk or where the mode of action clearly indicates negligible risk (e.g., viral or bacterial target, with no cross-reactivity with human tissues).[9]

- For products other than vaccines for infectious disease indications, an adequately designed enhanced pre- and post-natal development (ePPND) study in the NHP with fewer test article groups (e.g., one control group and one treated group) may be adequate to assess risk, provided the exposure achieved in the treated group provides saturation of

[6] See the ICH guidance for industry *S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals* (May 2021).

[7] See the ICH guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012) (ICH S6(R1)) and the guidance for industry *Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications* (February 2006).

[8] Ibid.

[9] See the guidance for industry *Development and Licensure of Vaccines to Prevent COVID-19* (June 2020).

target binding, maximal pharmacologic effect, and/or an adequate margin to clinical exposure.

- For indications where use of the product in women of childbearing potential is unlikely, it may be acceptable to collect embryo-fetal developmental and pre- and post-natal development data in the postmarketing setting.

- We recommend that sponsors discuss their proposed approaches to assessing DART endpoints, and their timing, with the appropriate review divisions before initiating any of the alternative DART assessments described in this guidance.