

*Contains Nonbinding Recommendations*

**COVID-19: Potency Assay  
Considerations for Monoclonal  
Antibodies and Other Therapeutic  
Proteins Targeting SARS-CoV-2  
Infectivity**

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**Guidance for Industry**

**January 2021**

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

# 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 (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 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 email request to [druginfo@fda.hhs.gov](mailto:druginfo@fda.hhs.gov) or [ocod@fda.hhs.gov](mailto:ocod@fda.hhs.gov) to receive an additional copy of the guidance. Please include the document number FDA-2020-D-1136 and complete title of the guidance in the request.

## Questions

For questions about this document, contact [COVID19-productdevelopment@fda.hhs.gov](mailto:COVID19-productdevelopment@fda.hhs.gov).

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# **COVID-19: Potency Assay Considerations for Monoclonal Antibodies and Other Therapeutic Proteins Targeting SARS-CoV-2 Infectivity**

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## **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.

Due to the current public health emergency, FDA is issuing this guidance to assist sponsors in the development of monoclonal antibodies (mAbs) and other therapeutic proteins<sup>1</sup> for use as COVID-19 therapeutics. A critical quality control measure for these products is the development and implementation of a potency assay(s)<sup>2</sup> adequate to ensure that each lot is consistently produced with the potency<sup>3</sup> necessary to achieve clinical efficacy and that such potency is maintained over the shelf life of the product. Typically, FDA engages with sponsors regarding their development of appropriate potency assays over the course of drug development; these

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<sup>1</sup> The term *protein* is one of the statutory categories of biological products (section 351(i)(1) of the Public Health Service Act (42 U.S.C. 262(i)(1))). Under 21 CFR 600.3(h)(6), a protein is any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size.

<sup>2</sup> See 21 CFR 610.10.

<sup>3</sup> Under 21 CFR 610.3(s), potency is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.

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interactions usually happen over a span of years. However, given the compressed development timelines associated with therapeutics intended to treat COVID-19, FDA is issuing this guidance to provide more detailed recommendations to drug developers with the goal of facilitating more complete submissions. 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.

This guidance applies only to mAbs and other therapeutic proteins<sup>4</sup> designed to bind to viral receptors on host cells, inhibit viral entry, and/or elicit Fc-mediated effector function. Vaccines, hyperimmune globulins, gene therapies, cell therapies, and convalescent plasma are not within the scope of this guidance.

The guidance describes how potency assay methods required for release and stability testing can be shown to assess comprehensively known or potential mechanism(s) of action of the product. Such methods should also be sufficiently sensitive to demonstrate lot-to-lot consistency.<sup>5</sup> In addition to release and stability methods, additional methods that demonstrate the biological function(s) of the product may be needed for characterization and comparability studies. The guidance describes methods that applicants should use to ensure the potency of mAbs and other therapeutic proteins proposed for use as anti-infective agents for COVID-19.<sup>6</sup>

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 (42 U.S.C. 247d(a)(2)). However, FDA expects that the recommendations set forth in this guidance will continue to apply outside the context of the current public health emergency. Therefore, following the termination of the public health emergency, FDA intends to revise and replace this guidance with an updated guidance that incorporates 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 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.

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<sup>4</sup> See 21 CFR 601.2(a)(3) and (4).

<sup>5</sup> See 21 CFR 610.10 and 21 CFR 211.165(e).

<sup>6</sup> This guidance only applies to certain products regulated by the Center for Drug Evaluation and Research. Manufacturers of vaccines and medical devices (i.e., in vitro diagnostics) should consult their center review offices regarding appropriate assays and methods for products regulated by the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health.

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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>7</sup> In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.<sup>8</sup>

The Agency anticipates receiving investigational new drug applications (INDs), requests for emergency use authorization (EUA),<sup>9</sup> and biologics license applications (BLAs) for mAbs and other therapeutic proteins designed to bind to viral receptors on host cells, inhibit viral entry, and/or elicit Fc-mediated effector function. Monoclonal antibodies and mAb cocktails are being developed to target SARS-CoV-2, mediate effector functions, or both. Monoclonal antibodies capable of neutralizing the virus block the binding of coronavirus spike proteins to host cell receptors (e.g., ACE2 for SARS-CoV-1 and SARS-CoV-2) and/or inhibit viral entry. These products are referred to as neutralizing mAbs. Some mAbs directed against SARS-CoV-2 mediate Fc-effector functions in addition to or instead of neutralizing virus entry. Other mAbs may target alternative cellular receptors or cellular proteins (e.g., transmembrane protease serine 2 (TMPRSS2)) that facilitate virus infection.

In addition to mAbs, other protein therapeutics intended to target SARS-CoV-2 entry could be developed. These include scaffold proteins, which are engineered to have similar mechanisms as neutralizing mAbs, bifunctional molecules engineered to interfere with different steps of virus entry, or recombinant ACE2 or ACE2-Fc fusion proteins, which serve as decoy receptors to

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<sup>7</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>8</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>9</sup> Information regarding EUAs that have been issued during the COVID-19 pandemic for mAbs or other therapeutic proteins can be found at <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization>. For more general information about EUAs, see the guidance for industry and other stakeholders *Emergency Use Authorization of Medical Products and Related Authorities* (January 2017). We update guidances periodically. 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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inhibit viral infectivity. As the science evolves, other novel proteins designed to inhibit SARS-CoV-2 entry may also be eventually identified and submitted to the Agency.

To ensure mAbs and therapeutic proteins' clinical effectiveness through product expiry, an applicant develops a method or methods to monitor the potency of the biological product. Potency assays for mAbs and therapeutic proteins are designed to measure the binding to viral receptors on host cells and the inhibition of viral entry, and/or to elicit Fc-mediated effector function. Potency assays are designed to reflect the biological activity of the biological product in vivo. Potency measurements from these methods are used to demonstrate that only product lots that meet defined specifications or acceptance criteria are administered during all phases of clinical investigation and following market approval.

All potency assays used for release testing must comply with applicable biologics and current good manufacturing practice regulations.<sup>10</sup> When evaluating the appropriateness of a potency assay for a specific mAb or other therapeutic proteins for treating or preventing COVID-19, FDA may consider various factors, including: (1) product characteristics, (2) manufacturing processes, (3) the stage of development in which the assay will be used, (4) the robustness of the sponsor's quality system, (5) the strength of the sponsor's risk-based quality assessment, and (6) the totality of the information provided by the applicant.

### **III. Discussion**

Sponsors developing mAbs or other therapeutic proteins for the treatment and/or prevention of COVID-19 should implement potency assays for release and stability testing specifically designed to demonstrate the biological function(s) of the product<sup>11</sup> and provide justification for how assays used for release and stability testing comprehensively measure known or potential mechanism(s) of action of the product. Sponsors should develop a manufacturing control strategy that will identify potential shifts in the product's critical quality attributes known to affect each known and/or potential mechanism of action and detect changes in the performance of the manufacturing process before beginning phase 3 trials.

Depending on the proposed mechanism(s) of action, one or more assays should be considered to support the control strategy for confirming the drug's potency.<sup>12</sup> If the mAb or other therapeutic protein has multiple mechanisms of action (e.g., neutralization and Fc-effector function), multiple potency assays should be used. All quality-control release methods, including key assays for demonstrating the mechanism(s) of action, should be shown to be suitable for their intended purposes during development and validated by the time of a BLA submission.<sup>13</sup> The

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<sup>10</sup> See, for example, 21 CFR 610.10 (regarding tests for potency for biological products); 21 CFR 211.165(e) (regarding the establishment and documentation of the accuracy, sensitivity, specificity, and reproducibility of test methods); and 21 CFR 211.194(a)(2) (regarding laboratory records of testing methods).

<sup>11</sup> See the ICH guidance for industry *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (August 1999).

<sup>12</sup> *Ibid.*

<sup>13</sup> See 21 CFR 211.165(e) and as described in the guidance for industry *Analytical Procedures and Methods Validation for Drugs and Biologics* (July 2015) and the ICH guidance for industry *Q2(R1) Validation of Analytical Procedures: Text and Methodology* (March 1995).

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quality-control release methods should be informed by the product characterization during development. This section provides examples of assays, depending on the mechanism(s) of action, that can be included as part of the overall control strategy.

### **A. Methods**

Although a binding assay is generally sufficient to serve as a potency assay at the IND stage of development, because it demonstrates binding between the mAb or therapeutic protein and its target, a binding assay assesses only one aspect of the potency of a product; therefore, sponsors should subsequently develop methods that more comprehensively monitor the proposed mechanism(s) of action of the products. These methods should be incorporated into drug substance and drug product release testing and stability protocols. Potency assays should be described, justified, qualified, and validated to support a BLA.

The guidance for industry and other stakeholders *Emergency Use Authorization of Medical Products and Related Authorities* describes the Agency's recommendations on the information that should be included in any request for an EUA. Data from one or more potency assays and available supporting information about the assay(s) contribute to the scientific evaluation of the potential effectiveness of mAbs and other therapeutic proteins in treating or preventing COVID-19; therefore, FDA recommends submitting any available data and information, relating to potency assays, to support a request for an EUA for these products.

This section addresses considerations for possible assays.

#### **1. Binding Assays**

For the purposes of this guidance, *binding assays* are defined as assays that monitor the binding between the mAb or other therapeutic protein and its target. These assays are established early in product development, typically in the form of an enzyme-linked immunosorbent assay (ELISA) or a surface plasmon resonance (SPR) assay. Product lots should be compared to an appropriately qualified in-house reference material and activity should be expressed as a percentage of the reference material value. Although helpful in the initial phases of development, these assays do not directly confirm the product's ability to inhibit the target protein's activity and should not be used in lieu of methods that confirm potency.

Although a binding assay demonstrates aspects of binding between the mAb or therapeutic protein and its target, this assay does not provide a comprehensive assessment of the product's mechanism of action. For products intended to inhibit SARS-CoV-2 spike protein binding to ACE2, rather than a binding assay, FDA recommends a potency assay that is a better reflection of the intended mechanism of action; for example, an inhibition assay, such as an inhibition



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ELISA,<sup>14</sup> or SPR. An inhibition assay should be designed to evaluate the inhibition of virus-receptor interactions and may be appropriate to conduct in a biosafety level (BSL)-2 lab.<sup>15</sup>

## **2. Viral Neutralization Assays**

In comparison to binding assays, in vitro viral neutralization assays more comprehensively confirm a mAb's or therapeutic protein's mechanism of action and potency in blocking viral entry into susceptible cells. Because of the potential importance to evaluating these products, the Agency recommends establishing an in vitro viral neutralization assay early in development. This type of assay can be useful for advancing development, quality control, and characterization of neutralizing mAbs and other products targeting viral entry. The SARS-CoV-2 cellular entry includes four steps:

- (1) Binding to the cell surface receptor ACE2
- (2) Proteolytic cleavage of the spike (S) protein (by TMPRSS2 and/or Cathepsin L)
- (3) Six-helix bundle formation leading to virus-cell fusion
- (4) Release of the viral capsid into the cytosol

Assays that assess the ability of the protein(s) to inhibit any of these steps are predominantly cell-based assays and typically involve the use of wild-type (wt) virus, pseudotyped virus, or pseudotyped virus-like particles (VLP). When considering which method to use, sponsors should select a method that best monitors the step the product is expected to target in the virus replication cycle. Although wt virus neutralization assays are considered the gold standard for in vitro potency assays, alternative methods may be acceptable. For example, a potency assay could be designed to characterize the effect of the product on a specific entry step (e.g., virus-cell fusion). Additionally, accessibility to BSL-2 versus BSL-3 laboratories, as well as challenges to qualifying critical reagents and validating the overall assay performance, should be considered in assay selection. For methods using transfected cell lines, sponsors should also address target cell viability and variability. Below is a list of assays that may be suitable for use as a potency assay, along with key considerations for each assay:

- **wt SARS-CoV-2 virus neutralization assays.** These assays (such as plaque reduction, TCID<sub>50</sub>, and microneutralization assay) involve working in a BSL-3 laboratory. If using wt SARS-CoV-2 virus, sponsors should determine virus titer and develop, aliquot, and store master and working virus stocks appropriately. Sponsors should provide details on the production, storage condition, and stability of virus stocks used in the assays in

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<sup>14</sup> Tan, CW, WN Chia, X Qin, P Liu, MI-C Chen, C Tiu, Z Hu, VC-W Chen, BE Young, WR Sia, Y-J Tan, R Foo, Y Yi, DC Lye, and DE Anderson, 2020, A SARS-CoV-2 Surrogate Virus Neutralization Test Based on Antibody-Mediated Blockage of ACE2–Spike Protein–Protein Interaction, *Nat Biotechnol*.

<sup>15</sup> Relevant biosafety considerations may be found in the National Institutes of Health's guidelines *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (April 2019) and *FAQs – Interim Laboratory Biosafety Guidance for Research with SARS-CoV-2 and IBC Requirements under the NIH Guidelines* available at <https://osp.od.nih.gov/biotechnology/nih-guidelines/>; and the Centers for Disease Control and Prevention's guideline *Biosafety in Microbiological and Biomedical Laboratories* available at <https://www.cdc.gov/labs/BMBL.html>.

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accordance with existing guidance on these topics.<sup>16</sup> The qualification of any new working stock should include the sequencing of the epitope.

- **Pseudotyped virus- or VLP-based assay.** An alternative to working with a wt virus is the implementation of pseudotyped virus-based methods. These methods should be performed under appropriate biosafety conditions.<sup>17</sup> Pseudotyped virions can be generated by replacing the surface glycoprotein(s) expressing gene of a less pathogenic virus (e.g., vesicular stomatitis virus) with the gene encoding the SARS-CoV-2 spike protein, creating engineered, replication-competent virions. Another approach is to generate fusion-competent, but replication-incompetent VLPs by co-transfecting producer cells (usually 293T cells) with a set of plasmids encoding the SARS-CoV-2 spike protein and a matrix protein(s) driving the VLP budding in trans. Retrovirus-based VLP packaging systems have already been adapted for SARS-CoV-2 spike protein pseudotyping.

During method development of a neutralization assay using a pseudovirus or VLP, sponsors should generate data demonstrating SARS-CoV-2 spike protein-mediated cell entry and describe the generation, isolation, purification, and concentration steps used to minimize lot-to-lot variability of the pseudovirus or VLP. Additionally, sponsors should address the following:

- The critical reagents (i.e., producer and target cell lines, and virion constructs, as well as controls (negative and positive)) used in the assay should be described. When qualifying these critical reagents, sponsors should demonstrate long-term stability and address possible variability associated with the transfected cells lines.
  - Attention should be given to the manufacturing, stability, and qualification of the pseudovirus or VLP, which is a critical reagent for the assay. Lot-to-lot variability of VLPs can be observed in the quantity of the VLPs and the activity of the VLP stock. Sponsors should demonstrate VLP lot-to-lot consistency is appropriately controlled.
- **Virus surface glycoprotein-mediated cell-cell fusion-based assays.** These assays can be used as an alternative to the pseudotyped virus- or VLP-based assays. Typically, the level of fusion between the virus surface glycoprotein expressing cells and the virus receptor expressing cells should be assessed using a reporter gene. The expression of the reporter construct is dependent on the successful fusion between the two cell populations. Alternatively, the level of syncytia formation or dye transfer also can be used to quantify cell-cell fusion. As with the pseudotyped virus-based assays, the following should be addressed:

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<sup>16</sup> See the References section for a list of guidances regarding analytical procedures, method validation, and documentation.

<sup>17</sup> Relevant biosafety considerations may be found in the National Institutes of Health's guidelines *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (April 2019) and *FAQs – Interim Laboratory Biosafety Guidance for Research with SARS-CoV-2 and IBC Requirements under the NIH Guidelines* available at <https://osp.od.nih.gov/biotechnology/nih-guidelines/>; and the Centers for Disease Control and Prevention's guideline *Biosafety in Microbiological and Biomedical Laboratories* available at <https://www.cdc.gov/labs/BMBL.html>.

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- The controls (negative and positive), cell lines, constructs, and reporter constructs used in the method should be described. When qualifying these critical reagents, sponsors should demonstrate their long-term stability and address possible variability associated with the transfected cells lines.
- How well the assay mimics viral-cell fusion should be described. For example, are certain conformational or environmental (e.g., pH) changes needed for fusion to occur?
- The testing platform to be used with the assay should be indicated.
- Defined quantitation criteria should be used regardless of whether a reporter construct, syncytia formation, or dye transfer is used to measure cell-cell fusion.

Given possible differences between wt virus neutralization assay(s) and the alternative methods mentioned above (pseudotyped virus neutralization methods, VLP-based methods, or virus surface glycoprotein-mediated cell-cell fusion-based assays), FDA recommends that sponsors provide information addressing how (or whether) the assay's results correlate with wt SARS-CoV-2 neutralization.

Although this section of the guidance focuses on neutralizing assays for products that block SARS-CoV-2 spike protein-mediated virus entry, the concepts described herein are applicable to the development of mAbs or proteins that block other steps in the virus replication cycle.

### **3. Fc-effector Function Assays**

In general, sponsors should assess mAbs for their ability to demonstrate Fc-mediated effector functions,<sup>18</sup> such as complement activity and binding to Fc $\gamma$  receptors. For anti-SARS-CoV-2 mAbs demonstrating Fc-effector functions, appropriate methods should be included as part of the specifications to ensure consistent mAb potency and functions. Fc glycosylation relevant to the mechanism of action should also be monitored and controlled throughout the product life cycle; FDA recommends including an Fc $\gamma$ RIIIa-mediated/natural killer cell antibody-dependent cell-mediated cytotoxicity assay, as that appears to be the most sensitive to changes in glycosylation.

For mAbs engineered to alter binding to Fc receptors and complement components, characterization studies should be conducted on a one-time basis to demonstrate the engineered mAb performs as designed. Fc-fusion proteins may also engage Fc receptors and complement components and thus should also be characterized for these potential effects or to confirm the intended effect of any Fc modifications. For example, the Agency recommends that ACE2-Fc

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<sup>18</sup> For more information on Fc-mediated effector functions, see, for example, Jiang, X, A Song, S Bergelson, T Arroll, B Parekh, K May, S Chung, R Strouse, A Mire-Sluis, and M Schenerman, 2011, Advances in the Assessment and Control of the Effector Functions of Therapeutic Antibodies, Nature Reviews; Drug Discovery 10:101-110.

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fusion proteins be characterized for their ability to carry out Fc-effector functions using methods similar to those for the characterization of neutralizing mAbs.

### **B. Additional Considerations**

Sponsors should address the following additional considerations when developing methods to monitor potency.

- When describing a potency assay, sponsors should ensure that the virus isolate, or spike proteins used reflect common isolates prevalent in the United States. Sponsors should discuss how the isolates or proteins were selected and whether they reflect the viruses currently in circulation. Sponsors also should provide either the full genome sequence(s) of the isolate(s) or GenBank ID(s).
- Whether using wt virus, pseudotyped virus, or VLPs, a master cell bank of producer cells should be appropriately qualified and used to generate a working bank of virus producer cells.
- Information and data submitted to support EUA requests and BLAs should describe how the methods used for release testing and stability program differ from those used to initially characterize the potency of the mAb or other therapeutic protein during earlier development. That includes, but is not limited to, reagents, testing site(s), and testing platform(s), if applicable, to conduct the assay in question.
- For mAb cocktails, release testing methods should include an identity method that demonstrates the presence of each individual mAb and a quantitative method verifying the ratio of the individual mAbs. The sponsor should ensure the ratio is consistent from lot to lot.
- Novel mechanisms of action that are not addressed in this guidance may be identified in the future. For mAbs or other therapeutic proteins with such novel mechanisms of action, sponsors should consult the Agency for further recommendations regarding potency assays for release and stability testing.<sup>19</sup>

## **IV. References**

### **Analytical Procedures, Method Validation, and Documentation-Related Guidances<sup>20</sup>**

- Guidance for industry *Analytical Procedures and Methods Validation for Drugs and Biologics* (July 2015)

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<sup>19</sup> See 21 CFR 610.10, 211.165(e), and 211.194(a)(2).

<sup>20</sup> We update guidances periodically. 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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- Guidance for industry *Bioanalytical Method Validation* (May 2018)
- ICH guidance for industry *M4Q: The CTD — Quality* (August 2001)
- ICH guidance for industry *Q2(R1) Validation of Analytical Procedures: Text and Methodology* (March 1995)
- ICH guidance for industry *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products* (July 1996)
- ICH guidance for industry *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (August 1999)

### **Centers for Disease Control and Prevention Guideline<sup>21</sup>**

- *Biosafety in Microbiological and Biomedical Laboratories*

### **Emergency Use Authorization Guidance<sup>22</sup>**

- Guidance for industry and other stakeholders *Emergency Use Authorization of Medical Products and Related Authorities* (January 2017).

### **ICH Guidance<sup>23</sup>**

- ICH guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009)

### **Literary References**

- Jiang, X, A Song, S Bergelson, T Arroll, B Parekh, K May, S Chung, R Strouse, A Mire-Sluis, and M Schenerman, 2011, Advances in the Assessment and Control of the Effector Functions of Therapeutic Antibodies, *Nature Reviews; Drug Discovery* 10:101-110.
- Tan, CW, WN Chia, X Qin, P Liu, MI-C Chen, C Tiu, Z Hu, VC-W Chen, BE Young, WR Sia, Y-J Tan, R Foo, Y Yi, DC Lye, and DE Anderson, 2020, A SARS-CoV-2 Surrogate Virus Neutralization Test Based on Antibody-Mediated Blockage of ACE2–Spike Protein–Protein Interaction, *Nat Biotechnol.*

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<sup>21</sup> Available at <https://www.cdc.gov/labs/BMBL.html>.

<sup>22</sup> We update guidances periodically. 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>23</sup> Ibid.

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### **National Institutes of Health Guidelines<sup>24</sup>**

- *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (April 2019)
- *FAQs – Interim Laboratory Biosafety Guidance for Research with SARS-CoV-2 and IBC Requirements under the NIH Guidelines*

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<sup>24</sup> Available at <https://osp.od.nih.gov/biotechnology/nih-guidelines/>.