Considerations for CMC Information to Support Emergency Use Authorization of Biotechnology Products

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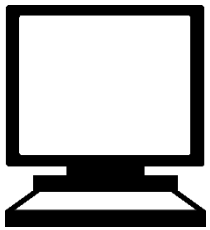
Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.



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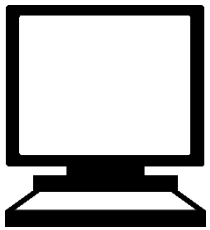



Drugs are no different.


FDA
Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.


It is what gives patients confidence in their *next* dose of medicine.

Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Emergency Use Authorization

- Permitted under Section 564 of the Federal Food, Drug, and Cosmetic (FD&C) Act, as amended by Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA)
- Authorization to make available unapproved uses of medical countermeasures (MCM) in response to emergencies involving chemical, biological, radiological, and nuclear (CBRN) agents, including infectious disease threats
- MCMs can include drugs, biologics, and devices
- Requires declaration from the HHS Secretary
- Terminated when circumstances that precipitated the declaration have ceased.

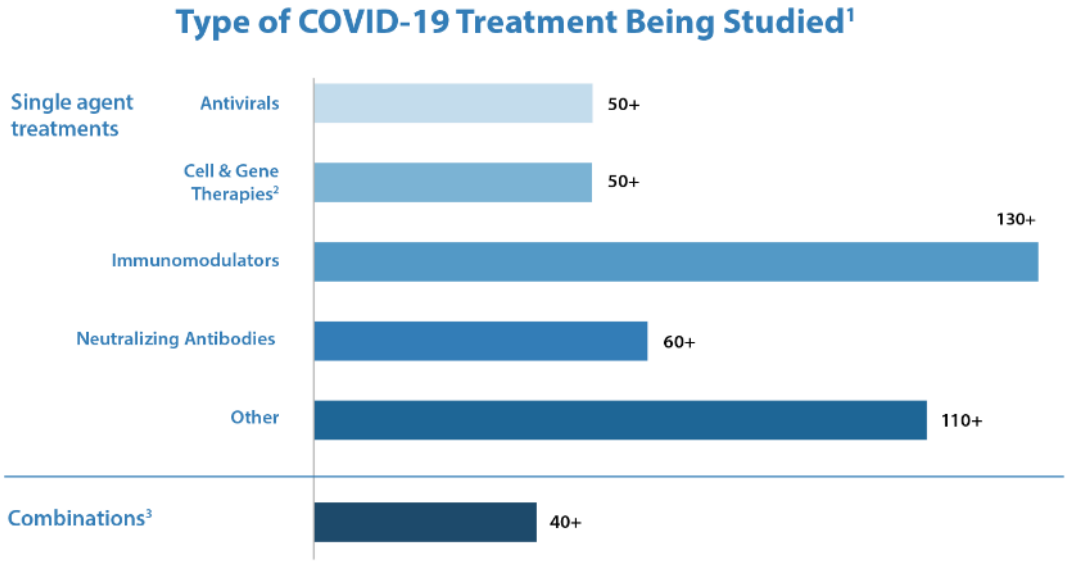
COVID-19 Public Health Emergency

- January 31, 2020 – Determination by HHS Secretary that a public health emergency exists;

- February 4, 2020 – Determination by HHS Secretary, pursuant to section 564 of FD&C Act, that there is a public health emergency that has significant potential to affect national security or the health and security of United States citizens living abroad;

- March 27, 2020 – Declaration by HHS Secretary that circumstances exist justifying the authorization of emergency use of drugs and biological products during COVID-19 pandemic

Coronavirus Treatment Activities

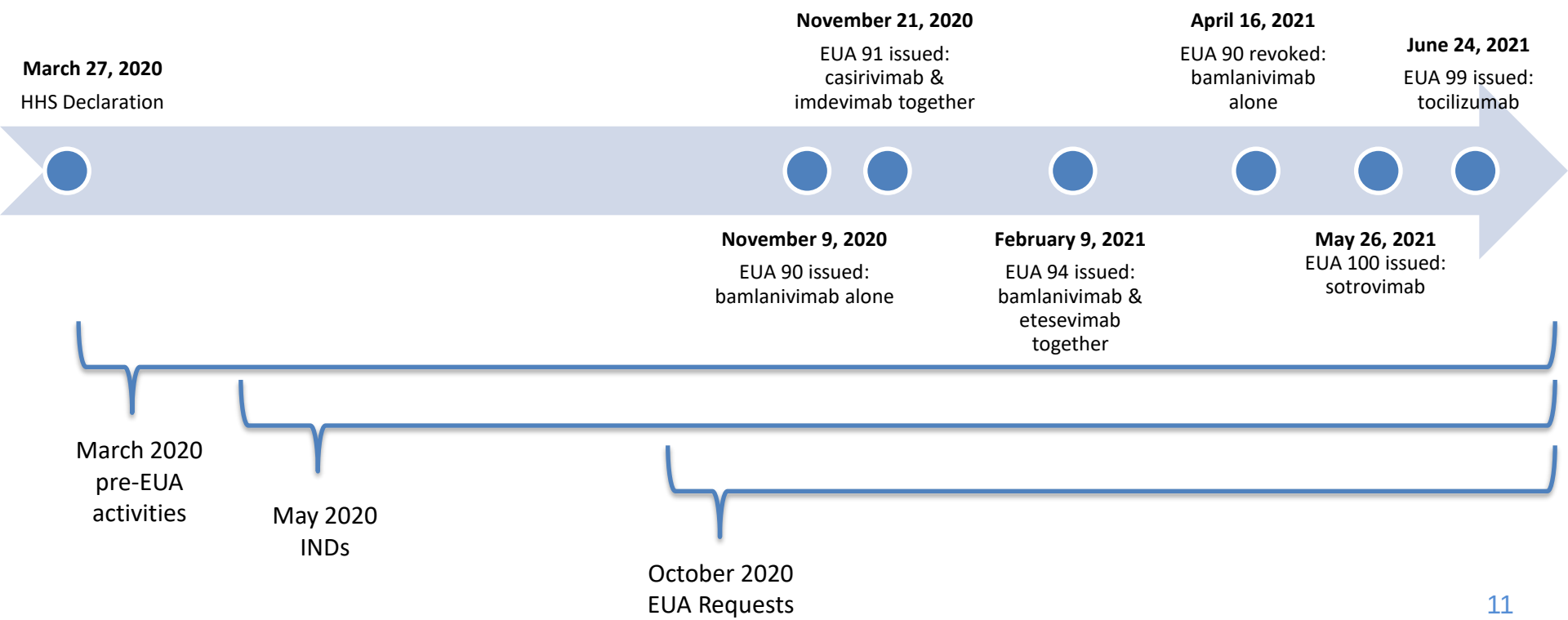


- > 630 development programs
- > 460 trials under IND
- 11 Emergency Use Authorizations
- 4 monoclonal antibody EUAs

This presentation is limited to biotechnology products. Other biologics, drugs, and devices are out of scope

Retrieved from https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap on August 13, 2021

COVID-19 Monoclonal Antibody EUA Timeline



Submission of CMC Information for EUA

- EUA requests may cross-reference existing applications (e.g., IND, BLA, or DMF) already on file for CMC information
  - Submission of an IND is not required for potential EUA products; however, this mechanism is generally anticipated for unlicensed EUA products
  - References to previously submitted CMC data should clearly indicate the specific information that is referenced and where it is located

- Early pre-EUA engagement with FDA to discuss CMC information is recommended:
  - Content and format of CMC information
  - CGMP compliance status of manufacturing and testing facilities that will manufacture emergency use materials
  - Manufacturing capacity, quantity of product on hand, surge capabilities

Refer to FDA guidance for industry, *Emergency Use Authorization of Medical Products and Related Authorities,* (January 2017).

Submission of CMC Information for EUA

- Conditions of an authorization may include additional reporting requirements and manufacturing conditions, such as (but not limited to):
  - Timely reporting of significant product quality problems, including information concerning change or deterioration in the distributed drug product
  - Compliance with CGMP
  - Restrictions on implementation of any changes to the description of the product, manufacturing process, facilities and equipment, and control strategy

- Manufacturing changes to an EUA:
  - Require advanced notice, concurrence, and authorization from the Agency
  - New manufacturing sites may warrant an inspection or site evaluation
  - Recommend advanced planning and communication with the Agency

Product Quality/CMC Expectations for EUA

"An EUA is not a long-term alternative to obtaining licensure of a monoclonal antibody therapy; therefore, sponsors should also design their development programs with the goal of providing adequate data to ultimately support licensure of their products under section 351 of the Public Health Services Act."— FDA guidance for industry, *Development of Monoclonal Antibody Products Targeting SARS-CoV-2, Including Addressing the Impact of Emerging Variants, During the COVID-19 Public Health Emergency* (February 20201).

Product Quality/CMC Expectations for EUA

Some guiding principles

Sufficient data and information to support:

- Safety and potency
- Lot-to-lot consistency
  - Sufficient control strategies
- Similar product quality profile between product used in the studies (e.g., clinical, virology, non-clinical) supporting the EUA and product for EUA use
- Stability and cold chain
- Dosing and preparation instructions
- Facilities with adequate compliance
- Adequate supply

Considerations – Facilities

"…a list of each site where the product, if authorized, is or would be manufactured, and the current CGMP status of the manufacturing site(s)"— FDA guidance for industry, *Emergency Use Authorization of Medical Products and Related Authorities* (January 2017).

- Include facility name, FEI number, and responsibilities for each manufacture and testing site of drug product and drug substance emergency use materials
- Consider selection of facilities that have experience and in manufacturing biotechnology products with history of inspections
  - Include recent inspection history (e.g., last 2 years)
  - Include inspection history from foreign agencies
- Consider timing of potential site inspection(s) or evaluations
  - Early communication of manufacturing plans with the Agency
- Include a statement that all facilities will comply with CGMP requirements

Refer to FDA guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers* (October 2019)

Considerations – Process Validation

"FDA may not require completed process validation (excluding sterilization process validation) to support an EUA"— FDA guidance for industry, *Development of Monoclonal Antibody Products Targeting SARS-CoV-2, Including Addressing the Impact of Emerging Variants, During the COVID-19 Public Health Emergency* (February 2021).

- Amount of process validation data needed may depend on risk/benefit considerations of the product
- Description of strategy to maintain process and product quality consistency throughout production of emergency use materials is expected
- Considerations for risk mitigation:
  - Extensive process characterization and product understanding (CQAs)
  - Additional process and product control elements (e.g., CPPs, IPCs, tests)
- Include future plans for process performance qualification

Considerations – Stability Data

- Stability- shelf life
  - Potentially challenging due to limited time to collect stability data
  - Supportive stability studies under accelerated and stress conditions
  - Potential to leverage other data (e.g., formulation development data, platform experience, related product data)
- Ongoing stability studies comprehensive for stability-indicating attributes (MOA)
- Conditions of authorization may include timely reporting of stability issues
- Consider shelf life that is appropriate to respond to the pandemic emergency

> *"Upon revocation of an EUA or its termination as a result of the termination of the HHS EUA declaration supporting it, an unapproved product or its labeling, and product information for an unapproved use of an approved product, must be disposed of pursuant to section 564(b)(2)(B) and (b)(3)"*— FDA guidance for industry, *Emergency Use Authorization of Medical Products and Related Authorities* (January 2017).

Considerations – Compatibility

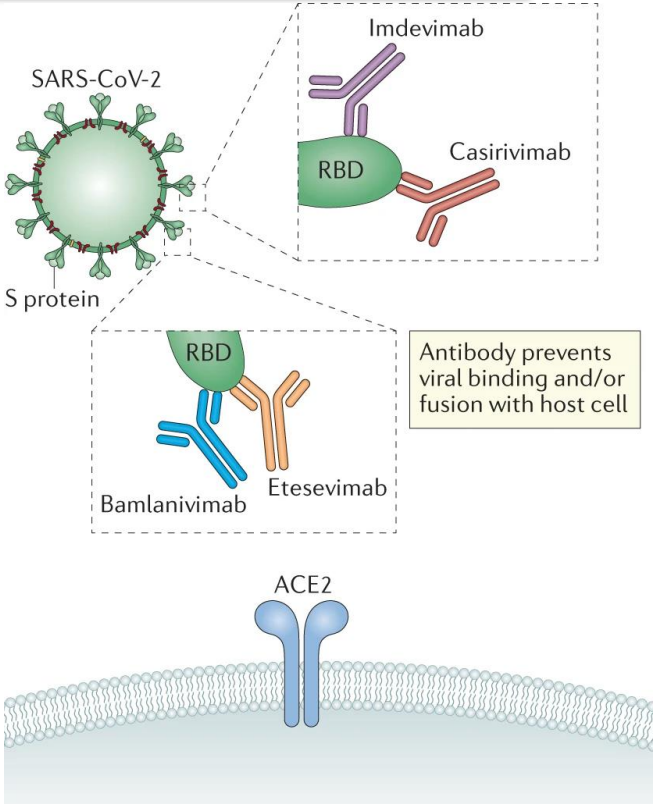
- In use conditions - practical considerations/flexibility
  - Consider potential shortage of infusion materials
  - Infusion materials -type
  - Infusion conditions (e.g., pump speed range, gravity)
  - Logistics at infusion sites
    - infusion time, preparation instructions, location of pharmacy and infusion center

➢ *Plan for data supporting robust in use conditions*

➢ *Carefully consider the route of administration and formulation*

Antiviral Neutralizing Antibodies

- Derived from B cells of convalescent cells
- Bind viral envelope proteins to sterically inhibit viral entry into host cells
- Antibodies to SARS-CoV-2 target the receptor binding domain (RBD) of spike (S) protein, thereby blocking interaction with the ACE2 receptor
- Antibody “cocktails” that recognize different epitopes on the RBD can mitigate risk from emerging variants



Taylor, P.C., Adams, A.C., Hufford, M.M. *et. al.* Neutralizing monoclonal antibodies for treatment of COVID-19. *Nat Rev Immunol* 21, 382-393 (2021).

Considerations – Potency assays

Target binding

- Examples:
  - direct binding to SARS-Cov-2 spike protein
  - inhibition of SARS-Cov-2 spike protein binding to ACE2 (preferred)
- Spike protein antigen is a critical reagent that should be adequately qualified
- Release and stability testing for the initial IND
- If not available at the time of IND submission, a relevant cell-base potency assay should be developed as development progresses (see next slide)

Refer to FDA guidance for industry, *COVID-19: Potency Assay Considerations for Monoclonal Antibodies and Other Therapeutic Proteins Targeting SARS-CoV-2 Infectivity Guidance for Industry* (January 2021)

Considerations – Potency assays

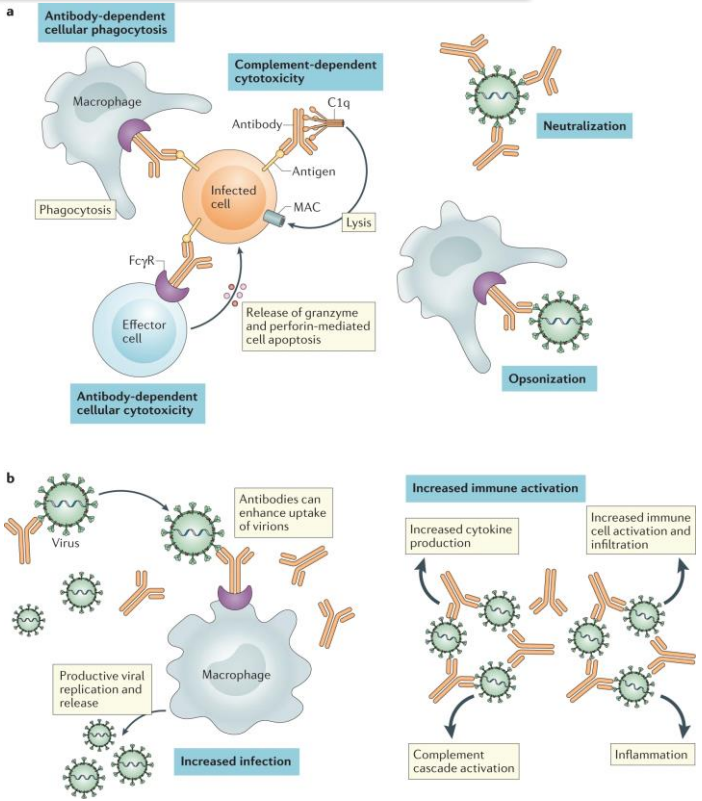
Cell-based virus neutralization

- Examples:
  1. wt SARS-CoV-2 virus neutralization. Needs a BSL-3 lab
  2. pseudotyped virus or VLPs. Can be done in a BSL-2 lab
  3. virus surface glycoprotein-mediated cell-cell fusion-based. Can be done in a BSL-2 lab
- Release and stability testing
- Justify how (or whether) results for assay formats 2 or 3 above correlate with wt SARS-CoV-2 neutralization

Refer to FDA guidance for industry, *COVID-19: Potency Assay Considerations for Monoclonal Antibodies and Other Therapeutic Proteins Targeting SARS-CoV-2 Infectivity Guidance for Industry* (January 2021)

Fc Effector Functions

- Potential Fc Effector Functions
  - Antibody-dependent cellular cytotoxicity (ADCC)
  - Antibody-dependent enhancement (ADE)
- MOA for some mAbs may include virus neutralization, antibody effector functions or both type of mechanisms
  - Potency assay should assess known or potential MOAs
- Animal models should demonstrate *in vivo* activity



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Considerations – Potency assays

Fc-effector function

- mAbs and fusion Fc-fusion proteins should be assessed for their Fc-mediated effector functions
  - mAbs with demonstrated Fc-effector functions should include an appropriate method in the specifications (e.g., FcγRIIIa-mediated/natural killer cell ADCC)
  - Should also monitor glycosylation profile relevant to the MOA
- mAbs engineered to reduce or abrogate binding to Fc receptors and complement components
  - One time characterization study to demonstrate the mAb performs as designed

Refer to FDA guidance for industry, *COVID-19: Potency Assay Considerations for Monoclonal Antibodies and Other Therapeutic Proteins Targeting SARS-CoV-2 Infectivity Guidance for Industry* (January 2021)

Considerations – Potency assays

Additional considerations

- Ensure the virus isolate or spike proteins used in the assay reflect common isolates prevalent in the US
  - Discuss how they were selected and whether they reflect the viruses currently in circulation
- Adequate qualification of the MCB & WCB of the wt virus, pseudovirus or VLPs producer cells
- Explain how the methods used for release and stability testing differ from the methods used to initially characterize the potency of the product (e.g., reagents, testing sites, etc)

Refer to FDA guidance for industry, *COVID-19: Potency Assay Considerations for Monoclonal Antibodies and Other Therapeutic Proteins Targeting SARS-CoV-2 Infectivity Guidance for Industry* (January 2021)

Variants of Concern

"FDA strongly recommends that individual monoclonal antibody products be developed with the expectation that they be combined with one or more monoclonal antibody products that bind to different epitopes to minimize the risk of losing activity against emergent variants."— FDA guidance for industry, *Development of Monoclonal Antibody Products Targeting SARS-CoV-2, Including Addressing the Impact of Emerging Variants, During the COVID-19 Public Health Emergency* (February 20201).

Emerging Variants – CMC Considerations

- Monoclonal antibody cocktails formulated in same primary container
  - Release testing should include methods that demonstrate identity and quantity of each antibody
  - Stability testing to support compatibility
- Monoclonal antibody cocktails formulated in separate containers
  - In-use stability compatibility studies
- Adapt potency assay formats (e.g., binding assays and neutralization assays) with revised reagents that evaluate new variant protein(s) or pseudotyped virus/virus-like particles
- Use available data from public consortia or partnerships that may contribute to understanding product performance
- Use of prior development experience to anticipate best dosage form, route of administration, and formulation (composition)

Additional Resources

- Guidance for industry, *COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention* (May 2021)
- Guidance for industry, *Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers* (May 2021)
- Guidance for industry, *Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency* (April 2021)
- Guidance for industry, *COVID-19 Container Closure System and Component Changes: Glass Vials and Stoppers* (March 2021)
- Guidance for industry, *Development of Monoclonal Antibody Products Targeting SARS-CoV-2, Including Addressing the Impact of Emerging Variants, During the COVID 19 Public Health Emergency* (February 2021)
- Guidance for industry, *COVID-19: Potency Assay Considerations for Monoclonal Antibodies and Other Therapeutic Proteins Targeting SARS-CoV-2 Infectivity* (January 2021)

Additional Resources

- Guidance for industry, *Review Timelines for Applicant Responses to Complete Response Letters When a Facility Assessment is Needed During the COVID-19 Public Health Emergency* (December 2020)
- Guidance for industry, *Resuming Normal Drug and Biologics Manufacturing Operations During the COVID-19 Public Health Emergency* (September 2020)
- Guidance for industry, *Good Manufacturing Practice Considerations for Responding to COVID-19 Infection in Employees in Drug and Biological Products Manufacturing* (June 2020)
- Guidance for industry, *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention* (May 2020)
- Guidance for industry, *Effects of the COVID-19 Public Health Emergency on Formal Meetings and User Fee Applications—Questions and Answers* (May 2020)
- Guidance for industry, *COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products* (May 2020)
- Guidance for industry, *Exemption and Exclusion from Certain Requirements of the Drug Supply Chain Security Act During the COVID-19 Public Health Emergency* (April 2020)
- Guidance for industry, *Notifying FDA of a Permanent Discontinuance or Interruption in Manufacturing Under Section 506C of the FD&C Act* (March 2020)

Acknowledgements

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