Regulatory Approaches to CMC Development During COVID-19: Challenges and Opportunities

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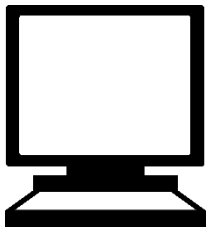
Pharmaceutical Quality

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



Pharmaceutical Quality

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

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

Please refer to any cited guidance, as this talk only refers to them at a high level. Specific regulatory issues need to be addressed with the relevant assessment team.

Outline

- FDA COVID-19 website
- Coronavirus Treatment Acceleration Program
- CDER pIND and IND process
  - CMC advice
- OBP flexibility for neutralizing antibodies to enter Phase 1 clinical trials
- Repurposed drugs
- COVID-19-related CMC guidance documents for drugs and biologics

FDA Information on COVID-19

- FDA has a central website for information related to COVID-19
  - https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19

- This website has links to COVID-19 related guidance documents, Frequently Asked Questions (FAQS), the Coronavirus Treatment Acceleration Program (CTAP) and other information useful to industry and the general public

Coronavirus Treatment Acceleration Program

- Uses every available method move new treatments to patients as quickly as possible, while at the same time finding out whether they are helpful or harmful.
- Dashboard provides a snapshot of the development of potential COVID-19 therapeutics

Does not include vaccines

560+

Drug development programs in planning stages[1]

STP INDs

370+

Trials reviewed by FDA[2]

8 ~~5~~

bamlanivimab
baricitinib
casirivimab/imdevimab

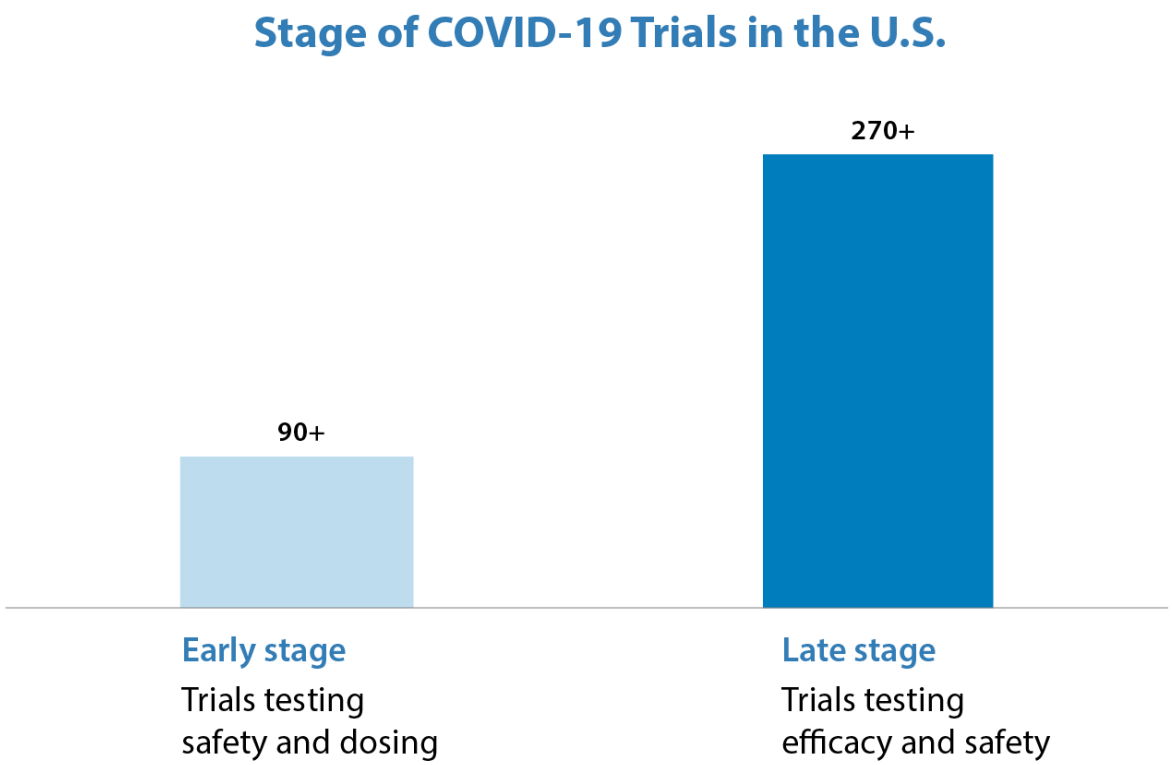
COVID 19 treatments currently authorized for Emergency Use[3]

1

Treatments currently approved by FDA for use in COVID-19

Data as of 10/31/2020

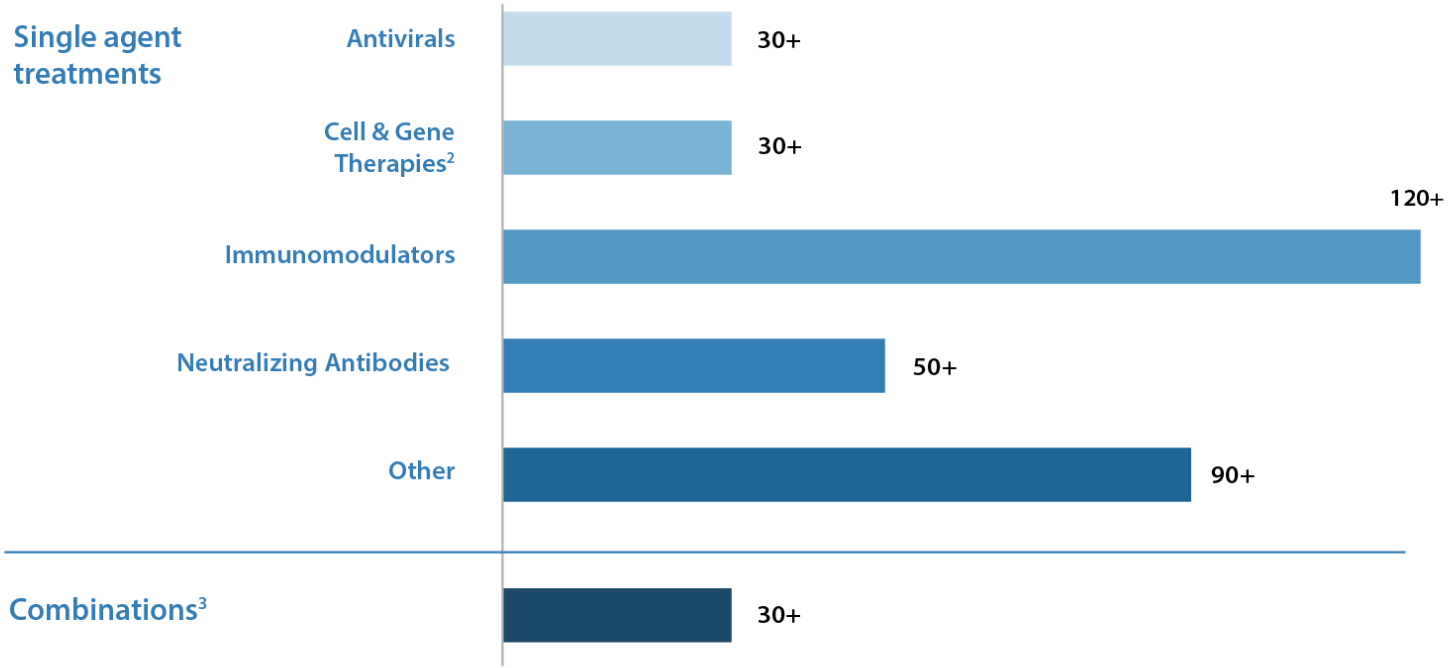
Coronavirus Treatment Acceleration Program



Data as of 10/31/2020

Coronavirus Treatment Acceleration Program

Type of COVID-19 Treatment Being Studied[1]



Data as of 10/31/2020

The pIND process in CDER

- See the Guidance for Industry and Investigators "COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products" (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-public-health-emergency-general-considerations-pre-ind-meeting-requests-covid-19-related)

- pIND requests can be submitted through the Electronic Submissions Gateway (ESG) or through the CDER NextGen Portal
  - Requests for products regulated by CBER should be sent to CBERDCC_eMailSub@fda.hhs.gov.

- To expedite communication, meeting background materials should be included with the meeting request

- The pIND request goes through a triage team to ensure the completeness and sufficiency of the information provided by sponsors for expedited review by review divisions.

https://www.fda.gov/drugs/coronavirus-covid-19-drugs/drug-development-inquiries-drugs-address-covid-19-public-health-emergency#submit

The pIND process in CDER

- The triage team will communicate with sponsors, if necessary, on any additional information needed for divisional assignment and review.
- Once information is determined to be sufficiently complete, the triage team will communicate a division assignment to the sponsor and forward the submission to the OND review division for expedited review.
- Most initial pINDs will be handled as Written Responses Only. The meeting request granted letter will provide a goal date for receiving the responses, but the OND divisions generally reply in a shorter time frame to help expedite development

https://www.fda.gov/drugs/coronavirus-covid-19-drugs/drug-development-inquiries-drugs-address-covid-19-public-health-emergency#submit

The IND process in CDER

- Submit as usual through the ESG
- A thorough pIND meeting package and discussion between the sponsor and FDA can lead to a more rapid review of the IND.
- For sponsors with products already in development under other INDs or licensed under a BLA, a new pIND/IND should be submitted for a proposed COVID-19 indication but the IND or BLA should be cross referenced.

https://www.fda.gov/drugs/coronavirus-covid-19-drugs/drug-development-inquiries-drugs-address-covid-19-public-health-emergency#submit

CMC-Related Advice in pIND Guidance Document

- Provide descriptions of
  - The active ingredient
  - Active ingredient manufacturing scheme
  - The formulation for clinical study
  - Dosage form and route of administration (ROA)
  - Known or suspected mechanism(s) of action

CMC-Related Advice in pIND Guidance Document

- Provide sufficient information to ensure acceptable quality (e.g., identity, purity, strength/potency) of the investigational drug for the intended phase of the drug development and data and information supporting stability of the drug for the duration of the clinical trial.

- For inhalational drugs, provide data to support the use of the drug for this ROA, including details of the formulation, devices for administration and appropriate GLP toxicology studies.

Declaration of Public Health Emergency

- On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.
- On March 13, 2020, the President declared a national emergency in response to COVID-19.
- 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.
- It is essential that the Agency receive key information that will help enable us to efficiently address proposals and ensure they are properly evaluated and managed in a timely manner.
- OBP is committed to these principles and will provide flexibility where possible to expedite the entry of therapeutic proteins into clinical trials.

OBP Flexibility to Expedite Entry of Neutralizing mAbs into Phase 1 Trials

- Principles laid out in the 1997 Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use were helpful
  - Reduced safety testing for feasibility clinical trials in serious or life-threatening conditions
  - Generic/modular virus clearance studies or
  - Two orthogonal robust virus clearance steps
- Platform processes and prior knowledge may provide support for less information than typically submitted in a non-pandemic IND.
  - OBP flexibility is contingent on this knowledge being shared with us and it should not be assumed that OBP will automatically accept less information
  - Expectation that other data be available as soon as possible – provide focused questions in pIND so review team can respond accordingly. May need subsequent communications for agreement on timing to submit information and data that may not be available at the time of IND submission
  - Novel approaches may be acceptable, but the Sponsor should anticipate the Agency's safety concerns and provide sufficient information justifying the novel approach

OBP Flexibility to Expedite Entry of Neutralizing mAbs into Phase 1 Trials

- Cell substrate changes during development
  - Initiating clinical trials with material manufactured before a clonally derived MCB is established using isogenic cell lines or stable pools
  - Materials manufactured from MCB no later than Phase 3, but earlier is preferable

- Risks for comparability between lots produced from stable pools and MCB
  - To reduce the risk associated with using materials derived from non-clonal stable pools, the FDA recommends developing an enhanced control strategy at the early stage of development.
  - For example (but not limited to): relatively narrow process parameter ranges, defined culture duration/population doubling time, additional in-process controls with stringent criteria/limits, DS specification that includes comprehensive CQA coverage and adequate control of post-translational modifications and Fc receptor binding, if applicable.

OBP Flexibility to Expedite Entry of Neutralizing mAbs into Phase 1 Trials

- Deferral of certain cell substrate and product testing
  - Submission of IND before all tests results are ready to be submitted
  - Test results submitted before 30-day deadline or commitment to not begin clinical study until safety testing is completed and results submitted, provided specifications (methods and acceptance criteria) are adequately described.

- Deferral of other information
  - Provide your timelines and justifications
  - Need agreement with review team for timing of submission relative to clinical development, submission of EUA or BLA

OBP Flexibility to Expedite Entry of Neutralizing mAbs into Phase 1 Trials – Potency Assays

- Use of target binding assay for release and stability to initiate IND with expectation to develop a relevant cell based potency assay as clinical development progresses
  - Most sponsors are using direct binding assays (mAb binding to SARS-CoV-2 spike protein)
  - An assay designed to demonstrate inhibition of SARS-CoV-2 spike protein binding to ACE2 is preferable to an assay that demonstrates direct binding to spike protein.
  - Spike protein antigen is a critical reagent that should be appropriately qualified
  - A relevant cell based assay should be developed during clinical development

Potency assays for nAbs – Virus Neutralization

- Cell-based Virus Neutralizing assays
  - No FDA expectation to use wild type SARS-CoV-2 based method (plaque reduction, $TCID_{50}$, microneutralization assays) as working with SARS-CoV-2 requires BSL-3 conditions.
  - Pseudotyped virus- or VLP-based assays are considered relevant for the purpose of release and stability testing.
    - Pseudotyped virus or VLPs are critical reagents that should be appropriately and stringently qualified, including stability studies for development of a robust assay
    - Note that some mAbs may not neutralize virus entry, but rather include antibody effector functions as their mechanism or utilize both mechanisms. Therefore, virus neutralization methods may not accurately reflect in vivo activity for some mAbs. However, in vivo activity should have been demonstrated in animal models (and will be requested by the Division of Antivirals).

Potency assays for nAbs – Antibody Effector Function

- All mAbs should be characterized for antibody effector functions
  - mAb mechanisms may include neutralizing activity and effector functions
  - CDC, ADCC, ADCP (if relevant), FcγR binding and ADE
  - If the mAb is engineered to reduce binding to FcγR, the reduction in binding should be demonstrated, generally on a one time basis.
  - If the nAb demonstrates effector functions, an appropriate cell based assay should be developed.
  - During early development it would be acceptable to control glycan species and FcγR binding for release and stability until an appropriate cell based assay is developed

CQA's associated with PK

- Characterization should include a method(s) to assess FcRn binding – crucial for comparability
- Glycan species, in particular high mannose, should be part of release testing – also crucial for comparability
- Some nAbs are engineered for an extended half life
  - Demonstrate the engineering accomplished its intended purpose
  - Some mAbs have V region glycosylation. If this glycosylation is not needed for binding, the sequence should be engineered out. There have been examples where the V region glycan species, which may be more highly sialylated than the Fc region glycan, could counteract the engineering for a longer half-life

Neutralizing mAbs and Manufacturing capacity

- If these products work, does the sponsor have adequate manufacturing capacity to manufacture enough product to treat COVID-19 patients?
  - Treatment and/or prophylactic?
- Are additional DS and DP manufacturing sites needed to increase capacity?
  - What are your plans to demonstrate comparability?
- Does the manufacturing of other commercial non-COVID-19 products need to be moved to other facilities to ensure enough capacity for COVID-19 products? If so, how quickly to avoid drug shortages?
- Please request a meeting with the CMC review team to discuss these concerns!

Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV): NIAID Clinical Trials for nAbs

- **Activ-2**- Launched in early July; Phase II/III outpatient trial of COVID-19 positive adults targeting enrollment of 110 patients per nAb in the Phase II portion and 900 patients per agent in the Phase III portion.
  - Bamlanivimab mAb enrolled.
  - Sponsors need their own IND before being enrolled in either ACTIV-2 or ACTIV-3 trial

- **Activ-3** – Launched in mid-July; hospitalized adult COVID-19 patients, 150 patients in the first stage and 506 patients in the second stage per nAb.
  - Bamlanivimab mAb enrolled.
  - Study arm closed due to low likelihood that the intervention would be of clinical value in the patient population

https://www.nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials

Repurposed drugs

- Many commercial products and products already in development for other indications are being studied to treat severe COVID-19
  - Anti-Viral (interferons)
  - Immunomodulators (either immunosuppressant or immunostimulatory)
  - Anti-thrombotic
- With an appropriate scientific rationale, these products can be introduced into COVID-19 clinical trials quickly.
- Since these drugs are already marketed or under IND, there should be few CMC concerns that would preclude initiating clinical studies, provided the ROA is the same as under BLA or previous IND.

Repurposed drugs – Commercial Products and Manufacturing capacity

- If these products work, does the sponsor have adequate manufacturing capacity to manufacture enough product to treat COVID-19 patients, as well as patients already treated under approved indications?
- Are additional DS and DP manufacturing sites needed to increase capacity?
  - What are your plans to demonstrate comparability?
- Does the manufacturing of other commercial non-COVID-19 products need to be moved to other facilities to ensure enough capacity for COVID-19 products? If so, how quickly to avoid drug shortages?
- Please request a meeting with the CMC review team to discuss these concerns!

Repurposed drugs – Clinical Products and Manufacturing capacity

- If these products work, does the sponsor have adequate manufacturing capacity to manufacture enough product to treat COVID-19 patients, as well as patients enrolled in clinical trials without interruption of their treatment?
- Provide a cross-reference to the original IND
  - If relevant sections in cross-referenced IND were in paper submissions, provide PDFs of this information (Module 3 and Module 4) to the COVID-19 IND or electronically update original IND
- Is the potency assay appropriate for the COVID-19 indication?
  - You may need to add a potency method that better reflects the proposed MOA in COVID-19
- Is there sufficient manufacturing capacity to support use under an EUA or BLA?
- Are additional DS and DP manufacturing sites needed?
  - Are adequate materials available to demonstrate comparability?
- Please request a meeting with the CMC review team to discuss these concerns!

Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV): NIAID Clinical Trials for Repurposed Drugs:

- **Activ-1** – Launched in late June; Phase III trial targeted to enroll about 2,000 patients over age 18 who have been hospitalized with a diagnosis of COVID-19.
  - It will test three host-targeted immune modulators against TNFα, CTLA-4 and CCR2/CCR5 as add on to remdesivir to assess illness severity, recovery speed, mortality and hospital resource utilization..
- **Activ-4** – Launched in September. Phase III trial of antithrombotics to prevent, treat, and address COVID-19-associated coagulopathy (CAC), or clotting.
  - apixaban and aspirin in outpatient setting, UF and LMW heparin in hospital, may be combined with ACTIV-1
- **Activ-5** – Big Effect Trial to evaluate whether certain approved therapies or investigational drugs in late-stage clinical development show promise against COVID-19.
  - Risankizumab (anti-IL23A) and lenzilumab (anti- CSF2) both in conjunction with remdesivir compared with placebo and remdesivir

https://www.nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials

Other potential CMC concerns

- Do you have an adequate raw material supply chain, including glass vials and stoppers?
- Communicate early with the review team regarding container and carton labeling for an EUA.
- Do you have a medically necessary drug (non-COVID-19) that may go into a Drug Shortage due to pandemic related supply chain, personnel or other reasons?
  - Please reach out to Drug Shortages Staff https://www.fda.gov/drugs/coronavirus-covid-19-drugs/drug-shortages-response-covid-19

CMC related guidance documents for drugs and biologics*

- Resuming Normal Drug and Biologics Manufacturing Operations During the COVID-19 Public Health Emergency; September 2020
- Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers; August 2020
- Temporary Policy for Manufacture of Alcohol for Preparation of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency (COVID-19) Guidance for Industry; August 2020 (plus 2 additional document related to hand sanitizer)
- Good Manufacturing Practice Considerations for Responding to COVID-19 Infection in Employees in Drug and Biological Products Manufacturing: June 2020

***additional CMC guidance documents may be published by the time of this presentation or afterwards**

CMC related guidance documents for drugs and biologics*

- Effects of the COVID-19 Public Health Emergency on Formal Meetings and User Fee Applications — Questions and Answers: May 2020
- COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products ; May 2020
- Exemption and Exclusion from Certain Requirements of the Drug Supply Chain Security Act During the COVID-19 Public Health Emergency: April 2020
- Notifying FDA of a Permanent Discontinuance or Interruption in Manufacturing Under Section 506C of the FD&C Act Guidance for Industry March 2020

***additional CMC guidance documents may be published by the time of this presentation or afterwards**

Operation Warp Speed

- US initiative to accelerate COVID-19 countermeasures
- Is only considering therapeutic candidates that could be authorized or approved, and produced at scale, this year
- Investing in repurposed drugs and new potential therapies that have undergone rapid preclinical development.
  - "investing in the candidates that are furthest along so that we could have products by early fall of 2020"
- Narrowing investments to potential therapies that can be manufactured at commercial scale this year.
  - "to see evidence that there is the technical and industrial capability to scale-up manufacturing rapidly to tens or hundreds of millions of doses for vaccines or hundreds of thousands of doses for therapeutics"
- Focused on therapies that provide passive immunity, including convalescent plasma and mAbs, as well as antivirals, as the "most promising options"
- Warp Speed has provided the funds to cover at-risk manufacturing

https://www.hhs.gov/coronavirus/explaining-operation-warp-speed/index.html

Thank you for your attention
ありがとうございます

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