Regulatory Approaches to Accelerated Development of SARS-CoV Neutralizing Antibodies and Vaccines

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These comments are an informal communication and represent our own best judgment. These comments do not bind or obligate FDA.
Biological Products Regulated by CBER

- Blood, blood components and derivatives (e.g. convalescent plasma)
- Vaccines (preventive and therapeutic)
- Tissues
- Cell and gene therapies
- Xenotransplantation
- Allergenics
- Related devices (including IVDs)
Products Regulated by CDER

Drugs – including
- Prescription (including generic)
- OTC

Therapeutic biological products – including (but not limited to):
- Monoclonal antibodies
- Therapeutic proteins
- Immunomodulators
- Growth factors
- Cytokines
Responding to Public Health Challenges

FDA has adapted to challenges through extraordinary efforts and proactive measures.

Many more meetings with sponsors to encourage/speed development of new products.
• Includes product sponsors, federal partners and other National Regulatory Agencies.

Inspections or site-visits of manufacturing facilities earlier in the process.

Careful attention to risk/benefit and risk management issues.
Approaches to Facilitate Product Availability or Approval/Licensure

- Early and frequent consultation between sponsor (or end user) and FDA
  - Type A, B, C meetings
  - INTERACT

- Mechanisms to make available for emergency use
  - Expanded access IND
  - Emergency Use Authorization (EUA)

- Expedited Programs
  - Fast Track
  - Priority Review
  - Breakthrough Therapy
  - RMAT

- Approval/Licensure Pathways
  - Accelerated Approval
  - Animal Rule
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Meetings with FDA

**Type A**
- Meetings that are necessary for an otherwise stalled product development program to proceed, or
- To address an important safety issue

**Type B**
- Pre-IND meetings
- EOP meetings
- Pre-EUA meetings
- Pre BLA/NDA meetings

**Type C**
- A meeting to discuss product development that is not a TYPE A or Type B
- Includes meetings to discuss Accelerated Approval endpoints

**INTERACT**
- Initial Targeted Engagement for Regulatory Advice on CBER products
- Informal, nonbinding advice provided early in development
- Replaces pre-pre IND meeting
Early and Frequent Consultation

- Improves communication process.
- Improves quality of laboratory and clinical studies.
- Reduces misunderstandings and likelihood of multiple review cycles.
- Improves efficiency of product development.
- Very resource intensive.
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Source: www.fda.gov
Expanded Access IND

**Individual patient – use under an emergency IND (eIND)**

- For use by a single patient
- Investigational product may or may not be under development
- Submitted as a protocol *under a new IND*
- Informed consent required per regulations

**Intermediate size Populations**

- For use by more than one patient, but generally fewer patients than are treated under a typical treatment IND
- The investigational product may or may not be under development for marketing
- Informed consent required per regulations

**Treatment IND**

- For wide-spread use of investigational products in an emergency
- Must be under active development for marketing
- Generally held by CDC, DoD or other USG entity
- Informed consent required per regulations
- Potentially cumbersome for wide-spread use
## Expanded Access for Convalescent Plasma (CP)

### Individual eIND
- Began arriving March 2020
- Sponsored by individual institutions/doctors
- By April 2020, receiving 100s of requests a day

### Mayo Expanded Access Program
- In response to overwhelming numbers of eINDs
- Sponsored by Mayo clinic
- Allowed > 100,000 access to CP
- Discontinued in August 2020 when EUA authorized
Emergency Use Authorization (EUA) Legislation

**Bioshield (7/2004)**
- Provided structure of EUA process
- Designed to allow mass vaccination during a PHE, such as the anthrax event of 2001
- Also allow for prepositioning of stockpiled MCMs in the SNS without violating PHS Act
- Covered chemical, biological, or radiological/nuclear agents (CBRN)

**PAHPRA (3/2013)**
- New authorities allow FDA to authorize use prior to an event

**Cures Act (2016)**
- Authorize emergency use of unapproved animal drugs or unapproved uses of approved animal drugs

**Public Law 115-92 (12/2017)**
- Added any agent(s) that might cause life-threatening injuries to US military personnel
EUA Authorization Process

**Determination**
By the Secretary of Homeland Security (DHS), Health and Human Services (HHS), or Department of Defense (DoD) that there is an emergency or potential for one. Or identification of a Material Threat by DHS Secretary.

**Declaration**
Based on a Determination, the HHS Secretary must declare that circumstances exist justifying the authorization. FDA guidance refers to this as an ‘EUA Declaration’.

**Authorization**
FDA may then issue an Emergency Use Authorization for an unapproved product or an unapproved use of an approved product.
EUA Authorization Process for COVID-19 pandemic

**Determination**
On February 24, 2020, the Secretary of Health and Human Services (HHS) determined that there is a significant potential for a public health emergency that involves the novel coronavirus (nCoV). .

**Declaration**
On March 27, 2020, the HHS secretary declared that circumstance exist justifying emergency use of drugs and biological products during the COVID-19 pandemic.

**Authorization**
CBER/CDER authorized products 8/23/20 through present.
Emergency Use Authorization (EUA)

- FDA can authorize use of an unapproved product or unapproved use of an approved product if:
  - CBRN agent can cause serious or life-threatening disease or condition;
  - The product may be effective;
  - Product’s known and potential benefits must outweigh known and potential risks; and
  - No adequate and sufficiently available approved alternative.

- EUA is granted until circumstances justifying emergency use have ceased or the product is approved/licensed for the proposed use.
COVID EUAs Authorized by CBER

- COVID Convalescent Plasma
- Pfizer COVID-19 vaccine
- Moderna COVID-19 Vaccine
- Janssen COVID-19 Vaccine
Traditional Vaccine Development

- Animal studies
- First studies in humans
- Safety and efficacy studies
- Large efficacy studies
- Vaccine administration
- Manufacturing process development
- Manufacturing process scale-up, validation
- Commercial-scale manufacturing
- Post-approval surveillance
- Licensure
Accelerated Vaccine Development

Compare vaccines in extensive animal studies

Human safety and efficacy studies

Emergency Use Authorization

Vaccine administration

Commercial-scale manufacturing

Licensure

Process development, scale-up to commercial production at risk

Establish vaccine distribution and administration infrastructure

Post-approval surveillance

Commercial-scale manufacturing

Clinical data collection & analysis
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Expedited Programs available during product development

Fast Track, Breakthrough Therapy, RMAT

Common elements:

- Unmet medical need in the treatment of a serious condition
- Submitted with IND or after, but before BLA/NDA submission
- FDA must respond to request within 60 days of request
Fast Track Designation

Typically granted during IND process, ideally no later than the pre-BLA/NDA meeting.

Applies to development program for a specific indication.

Product must be for serious or life-threatening condition and demonstrate potential to address an unmet medical need based on clinical or non-clinical data or has been designated as a qualified infectious disease product.

If granted, allows for more frequent meetings and correspondence and a rolling submission of BLA/NDA.
Breakthrough Therapy

Typically granted during the IND process, ideally no later than the end-of-phase 2 meeting.

Applies to the product (alone or in combination) and the specific indication.

Preliminary clinical evidence indicates the product may demonstrate substantial improvement on a clinically significant endpoint over available therapies.

Intensive guidance on efficient drug development, rolling review, and other actions to expedite review.

The statute requires clinical evidence of a treatment effect; therefore, generally not applicable to the Animal Rule.
Regenerative Medicine Advanced Therapy (RMAT) Designation

<table>
<thead>
<tr>
<th>Requirements</th>
<th>RMAT designation provides</th>
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<tbody>
<tr>
<td>• Product must be a regenerative medicine therapy (which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product)</td>
<td>• All breakthrough therapy features, including early interactions to discuss any potential surrogate or intermediate endpoints</td>
</tr>
<tr>
<td>• Product is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition</td>
<td>• Possible priority review and accelerated approval (if eligible)</td>
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<tr>
<td>• Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition</td>
<td>• Statutory flexibility with regard to accelerated approval and post-approval requirements</td>
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</tbody>
</table>
Priority Review

- Expedited program granted at time of BLA/NDA submission.
- Product eligible if it provides treatment where no adequate therapy exists or if it provides significant improvement:
  - In safety or effectiveness of treatment, diagnosis, or prevention of serious or life threatening disease (biologics).
  - Compared to marketed products in treatment, diagnosis, or prevention of disease (drugs).
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Accelerated Approval

- Product eligible if it provides a meaningful therapeutic benefit over existing treatments for serious or life-threatening illness.
- Efficacy based on surrogate endpoints likely to predict clinical benefit (314.510, 601.40).
- Post-licensure/post-approval studies required (usually ongoing) to demonstrate effects on outcomes.
- Withdrawal if agreements violated/not S&E.
- Can approve through regular mechanisms with validated surrogate.
Animal Rule

New Drug and Biological Products: Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible.

It is NOT a simplified or expedited development process.

Does not apply if approval can be based on efficacy standards elsewhere in FDA regulations.
Risk/Benefit for MCMs

- Risk/benefit differs and FDA assesses for each product & potential use.
  - Treatment: For otherwise untreatable serious illness, reasonable to tolerate significant risk & some uncertainty.
  - Prophylaxis: If given to individuals before event or, post-event, to individuals who may not be at risk, balance shifts.
- All such products:
  - Need transparent, balanced and effective risk communication; may be challenging in emergencies.
Thank you!

- Manufacturer’s assistance (CBER):
  - Phone – (240)402-8010 or (800) 835-4709
  - http://www.fda.gov/cber/manufacturer.htm
Resources
FDA Websites

- Expanded Access INDs [https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm](https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm)
- RMAT designation [https://www.fda.gov/biologicsbloodvaccines/cellulargenetherapyproducts/ucm537670.htm](https://www.fda.gov/biologicsbloodvaccines/cellulargenetherapyproducts/ucm537670.htm)
COVID Guidance Documents

• COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders | FDA
• Emergency Use Authorization for Vaccines to Prevent COVID-19 | FDA
• COVID-19: Developing Drugs and Biological Products for Treatment or Prevention | FDA
• Investigational COVID-19 Convalescent Plasma | FDA
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>NDA</td>
<td>New Drug Application</td>
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<tr>
<td>OTC</td>
<td>Over the Counter</td>
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<tr>
<td>BLA</td>
<td>Biologics License Application</td>
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<tr>
<td>CTAP</td>
<td>Coronavirus Treatment Acceleration Program</td>
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<tr>
<td>EUA</td>
<td>Emergency Use Application</td>
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<tr>
<td>PDUFA</td>
<td>Prescription Drug User Fee Act</td>
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<tr>
<td>IVD</td>
<td>In vitro Diagnostics</td>
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<tr>
<td>COVID</td>
<td><strong>CO</strong>rona <strong>VI</strong>rus <strong>D</strong>isease</td>
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<tr>
<td>IND</td>
<td>Investigation New Drug</td>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
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<tr>
<td>CBRN</td>
<td>Chemical Biological Radiological Nuclear</td>
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<td>RMAT</td>
<td>Regenerative Medicine Advanced Therapy</td>
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<tr>
<td>PAHPRA</td>
<td>Pandemic and All-Hazards Preparedness Reauthorization Act</td>
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<td>MCM</td>
<td>Medical Countermeasure</td>
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<td><strong>IN</strong>itial <strong>Targeted Engagement for Regulatory Advice on CBER produ</strong>CTs</td>
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<td>Center for Biologics Evaluation and Research</td>
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<tr>
<td>CDER</td>
<td>Center for Drugs Evaluation and Research</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>DHS</td>
<td>Department of Homeland Security</td>
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<tr>
<td>USG</td>
<td>United States Government</td>
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<tr>
<td>HHS</td>
<td>Health and human Services</td>
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<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<tr>
<td>DoD</td>
<td>Department of Defense</td>
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<tr>
<td>EOP</td>
<td>End of Phase</td>
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